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## Original Communications

# THE EFFECT OF ORAL FEEDING AT DIFFERENT LEVELS ON THE ABSORPTION OF FOODSTUFFS IN INFANTILE DIARRHEA

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THE incidence of infantile diarrhea has greatly decreased in this country during the past half century, and advances in therapy, particularly in regard to the administration of parenteral fluids and parenteral alimentation, have greatly reduced the mortality rate. Nevertheless diarrheal disease continues in our midst, showing periodic outbreaks, and even under the best of conditions fatalities have not been eliminated. It has been our impression that nutritive failure was responsible for most of the fatalities. Since the best parenteral nutrition is not ideal, it occurred to us that oral nutrition was perhaps not being used to the greatest advantage and that the possibility of using it to better advantage deserved careful study. It seemed desirable in particular to investigate the current practice of early therapeutic starvation.

The policy of sharply reducing the oral intake or eliminating oral food entirely at the onset of the attack with a very cautious and gradual increase after a period of days has been the generally accepted procedure both in this country and abroad. When an increasing oral intake was followed by an exacerbation of the diarrhea it was generally assumed that the food was increased too rapidly, and a second period of therapeutic starvation was tried and sometimes even a third. This regimen is based on theoretical concepts that have never been critically tested. Our predecessors placed their reliance on the appearance and number of stools as the criterion of success of treatment, and since withholding food reduced the volume and frequency of the stools it was assumed that this was beneficial. This point of view was sharply challenged in 1924 by Park,[1] who maintained that the child rather than the stools should be taken as the criterion for evaluating therapy. Although his point of view has been influential in pediatric thinking, the fact remains that changes in the stools are more readily assessed than changes in the clinical state of the patient; the possible benefit

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from increased feeding is not insufficiently apparent to outweigh the emotions engendered in the spectators by an increased number of stools, and the stools still tend to dominate therapy.

A second theoretical consideration that has favored therapeutic starvation is the belief that food will stimulate digestive secretions and in the presence of severe peristalsis these secretions will be carried out, resulting in a net loss of electrolytes to the body. Whether or not such a net loss is induced by food in severe diarrhea is not actually known. Finally there is a belief that the withdrawal of food is beneficial by resting the intestine, which is thought to hasten recovery. This again has never been convincingly demonstrated.

It appeared to us that the value of therapeutic starvation could be accurately assessed by two studies: (1) a metabolic study of the assimilation of the various nutrients at different levels of feeding, which would show whether the restriction of food favors or decreases assimilation; and (2) a statistical study of patients treated alternately by therapeutic starvation and by full feeding, in which the clinical course of the illness was compared. The present communication deals with such a metabolic study. A succeeding report[2] describes such a clinical study.

## EXPERIMENTAL

*Subjects.*—The subjects employed for this study were male infants who were admitted to the Children's Medical Service of Bellevue Hospital for the treatment of diarrhea or who developed the disease on the ward. They varied from 12 days to 3 months in age and weighed from 2.5 to 5.3 kilograms. Enteric pathogens were not cultivated from the stools in any instance, and although attempts to establish a virus etiology were not made, it was believed that parenteral infection was responsible for the diarrhea in these patients. Initially all presented a picture of dehydration, acidosis, and toxicity of varying degree, which required restorative measures with parenteral fluids. Immediately after parenteral fluid administration the infants were transferred to the metabolism ward, where they were placed on frames for the separate collection of urine and feces.

*Metabolism Periods.*—An inherent difficulty in making comparisons of different diets is the possibility that the severity of the diarrhea may be altered during the period of study by factors quite apart from the food. It is obviously impossible to compare two successive experimental diets when the diarrhea is spontaneously waxing or waning; the diarrhea should be of comparable severity at the start and at the close of the observations. Since most of the diarrheas were of relatively short duration this necessitated short metabolism periods. We found it necessary to employ metabolism periods of only twenty-four hours' duration in order to make two or three observations on each subject before the picture had changed, and a number of subjects upon whom work had been started had to be eliminated because of obvious change in the status of the disease before a second period could be completed. Data were eventually obtained on six infants in whom the severity of the process was comparable. A metabolism period as short as twenty-four hours would not be suitable for most purposes because of irregularity and possible delay in intestinal evacuations; in the case of severe diarrhea, however, short periods do not involve this difficulty.

The feedings given during each period consisted of evaporated milk, corn syrup, and water, in proportions and concentrations comparable to those in daily use on the wards. This was done deliberately because it was thought advisable to judge the efficacy of a food which is commonly employed and of proved digestibility rather than to use a formula altered in composition and proportions on which claims for superior absorption might be made on the basis of our study. Infants were given a low caloric formula (30 to 45 calories per kilogram of body weight) or were completely starved, followed by a medium (60 to 69 calories per kilogram) or a full caloric formula (100 to 137 calories per kilogram). In some instances the higher feeding was given first. Apart from the measured amount of evaporated milk formula, the infants were offered water freely, but if clinical evidence of water deficit was present it was made up by parenteral 5 per cent dextrose in water. The beginning and end of each test period was identified in the stool by charcoal or carmine, which had been added earlier to the formula. At the end of the study period the infants were given parenteral fluids if needed and maintained on full caloric feedings until complete recovery took place as evidenced by complete cessation of diarrheal stools and progressive gain in weight for at least one week.

*Analysis of Food and Excreta.*—Aliquots of food, urine, and dried feces were analyzed for ash, sodium, potassium, chloride, calcium, fat, and nitrogen. The analytical procedures employed are listed.[3-8]

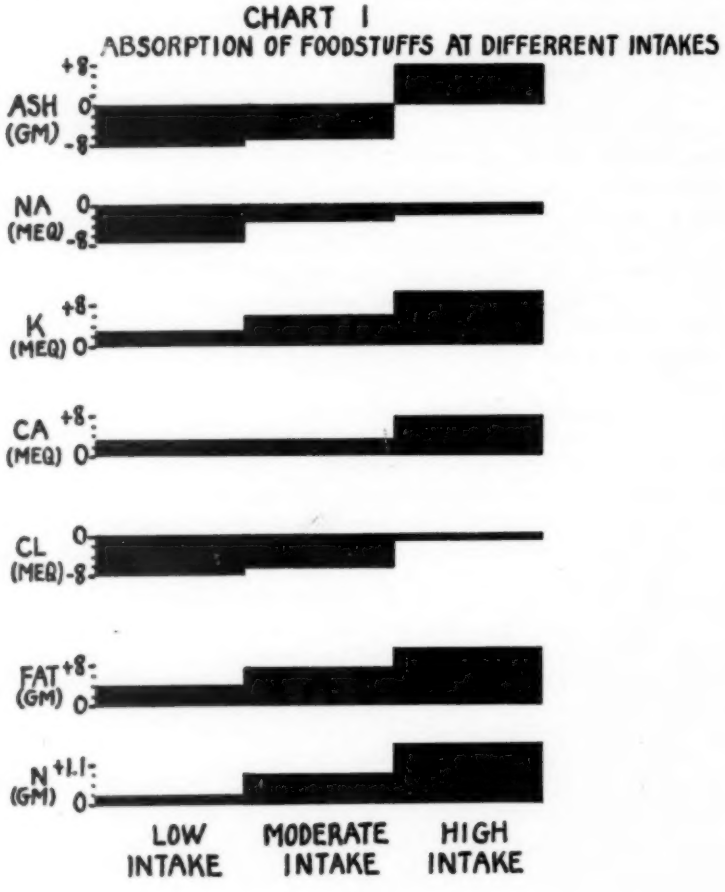
## RESULTS

Of a total of twenty-one patients with infantile diarrhea transferred to the metabolism ward for study, complete metabolic data were obtained on six. Brief protocols of these six with tabulated results and absorption charts are presented.

CASE 12.—R. H. was a 10-week-old white male infant admitted June 6, 1946, because of acute bronchitis. One week later he developed an otitis media and a mild diarrhea which became progressively worse. Treatment had consisted of parenteral physiologic saline and reduced oral food. He was transferred to the metabolism ward three days after the onset of diarrhea and appeared alert, hungry, and fairly well hydrated although he was having twelve watery movements a day. He was offered a formula of 30 calories per kilogram of body weight for the first twenty-four-hour period. The next day he had lost 200 Gm. and looked moderately dehydrated and less active. The second and third test periods provided 60 and 100 calories per kilogram for the intake respectively. A weight loss of 150 Gm. was sustained between these two periods; however, there was no further weight loss while he was maintained on 110 calories per kilogram, and ten days later the diarrhea subsided completely and he began to gain weight progressively. The only parenteral fluids necessary while under our observation were 320 c.c. of equal parts of normal saline and 5 per cent dextrose, given immediately after the metabolic observations were completed. A summary of the data is shown in Table I. Absorption values for all the food constituents investigated are shown in Chart 1.

CASE 26.—R. P. was a 12-day-old white male infant who developed a gradually progressive diarrhea on the third day of life. He was a small, poorly

nourished, moderately dehydrated infant, who had small green watery evacuations numbering seventeen to twenty per day. Initial hydration with parenteral saline and sodium lactate solutions was followed by three test periods on the metabolism frame, the data from which are shown in Table II and Chart 2. The infant was unable to maintain himself in water balance by oral fluids alone, and




5 per cent dextrose in water had to be given parenterally during each of the three test periods. He was maintained on 120 calories per kilogram by mouth with parenteral fluid supplements when necessary. On the ninth day after admission the diarrhea subsided, and he thereafter gained steadily in weight.

CASE 22.—L. H. was a 6-week-old white male infant admitted Nov. 9, 1946, with a two-week history of cough, cold, and diarrhea, the latter becoming increasingly worse. He had a purulent discharge from the right drum on admission. Group A hemolytic streptococcus was isolated from the discharges of the

nose, throat, and right ear, and on one occasion from the blood stream. Prior to transfer to the metabolism ward he had received lactate Ringer's solution parenterally and a reduced feeding orally. Data on two test periods with intakes of 45 calories per kilogram and 100 calories per kilogram were obtained as shown in Table III and Chart 3. At the end of the first period the infant looked moderately dehydrated, which finding was supported by marked oliguria and

CHART 2

ABSORPTION OF FOODSTUFFS AT DIFFERENT INTAKES

a weight loss of 195 Gm. During the next period, water was forced between feedings and the baby was very closely watched. Although the urinary flow improved somewhat he appeared apathetic and was markedly dehydrated, so it was decided to introduce fluids parenterally. Because of an error, 100 c.c. of normal saline instead of 5 per cent dextrose was given. After the end of the second test period the baby received vigorous parenteral fluid therapy and was maintained on 110 calories per kilogram of oral food. Four days later his diarrhea subsided completely, and he was showing daily gains in weight.

TABLE I. CASE 12

| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| Low Intake (30 cal./kg.) | Oral intake | 735 | 1.20 | 4.0 | 5.9 | 9.8 | 4.4 | 5.90 | 0.82 | 5.34 |
| | Urine | 370 | * | 0.1 | 13.8 | 2.4 | 12.1 | | 0.74 | |
| | Feces | 208 | 2.02 | 19.3 | 3.0 | 3.2 | 19.8 | 1.65 | 0.49 | |
| | Absorbed | +572 | −0.82 | −15.3 | +2.9 | +6.6 | −15.4 | +4.25 | −0.33 | |
| | % Intake absorbed | +72 | −68 | −380 | +50 | +68 | −349 | +72 | +40 | |
| Moderate Intake (60 cal./kg.) | Oral intake | 1005 | 2.40 | 8.0 | 11.8 | 19.6 | 8.8 | 11.80 | 1.64 | 5.14 |
| | Urine | 175 | * | 0.1 | 11.9 | 1.6 | 1.4 | | 0.69 | |
| | Feces | 267 | 3.08 | 13.0 | 5.4 | 13.0 | 22.2 | 3.86 | 0.82 | |
| | Absorbed | +738 | −0.68 | −5.0 | +6.4 | +6.6 | −13.4 | +7.94 | +0.82 | |
| | % Intake absorbed | +74 | −22 | −62 | +55 | +34 | −150 | +67 | +50 | |
| High Intake (100 cal./kg.) | Oral intake | 840 | 3.84 | 12.7 | 18.9 | 30.0 | 14.2 | 18.90 | 2.62 | 4.99 |
| | Urine | 87 | * | 0.1 | 14.0 | 0.9 | 0.8 | | 0.79 | |
| | Feces | 275 | 3.21 | 16.8 | 8.0 | 15.0 | 16.9 | 7.60 | 0.96 | |
| | Absorbed | +565 | +0.59 | −4.1 | +10.9 | +15.0 | −2.7 | +11.30 | +1.66 | |
| | % Intake absorbed | +67 | +16 | −32 | +59 | +50 | −19 | +60 | +63 | 4.99 |

*Ash in urine not determined.

TABLE II. CASE 26

| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| Low Intake (32 cal./kg.) | Total intake | 560* | 0.56 | 2.0 | 3.0 | 4.6 | 2.4 | 2.62 | 0.41 | 2.59 |
| | Urine | 190 | 0.16 | 0.3 | 14.0 | 0.3 | 4.5 | | 0.24 | |
| | Feces | 111 | 1.09 | 10.3 | 3.6 | 4.2 | 5.7 | 1.36 | 0.30 | |
| | Absorbed | +449 | −0.53 | −8.3 | −0.6 | +0.4 | −3.3 | +1.26 | +0.11 | |
| | % Intake absorbed | +80 | −95 | −420 | −22 | +9 | −135 | +48 | +27 | |
| Moderate Intake (64 cal./kg.) | Total intake | 1210† | 1.12 | 4.0 | 6.0 | 9.2 | 4.8 | 5.24 | 0.82 | 2.52 |
| | Urine | 430 | 0.19 | 0.3 | 13.5 | 0.2 | 5.7 | | 0.23 | |
| | Feces | 202 | 1.60 | 8.2 | 4.1 | 6.7 | 4.8 | 3.20 | 0.49 | |
| | Absorbed | +1008 | −0.48 | −4.2 | +1.9 | +2.5 | 0 | +2.04 | +0.33 | |
| | % Intake absorbed | +83 | −43 | −104 | +30 | +27 | 0 | +39 | +40 | |
| High Intake (128 cal./kg.) | Total intake | 810‡ | 2.24 | 8.0 | 12.0 | 18.4 | 9.6 | 10.48 | 1.64 | 2.55 |
| | Urine | 355 | 0.53 | 0.5 | 19.5 | 1.5 | 15.4 | | 0.35 | |
| | Feces | 151 | 1.64 | 8.9 | 3.9 | 14.9 | 3.3 | 4.30 | 0.43 | |
| | Absorbed | +659 | +0.60 | −0.9 | +8.1 | +3.5 | +6.3 | +6.18 | +1.21 | |
| | % Intake absorbed | +81 | +27 | −11 | +62 | +19 | +53 | +59 | +74 | 2.57 |

*Represents addition of 100 c.c. of 5 per cent dextrose parenterally to oral intake.
†Represents addition of 670 c.c. of 5 per cent dextrose parenterally to oral intake.
‡Represents addition of 300 c.c. of 5 per cent dextrose parenterally to oral intake.

TABLE III. CASE 22

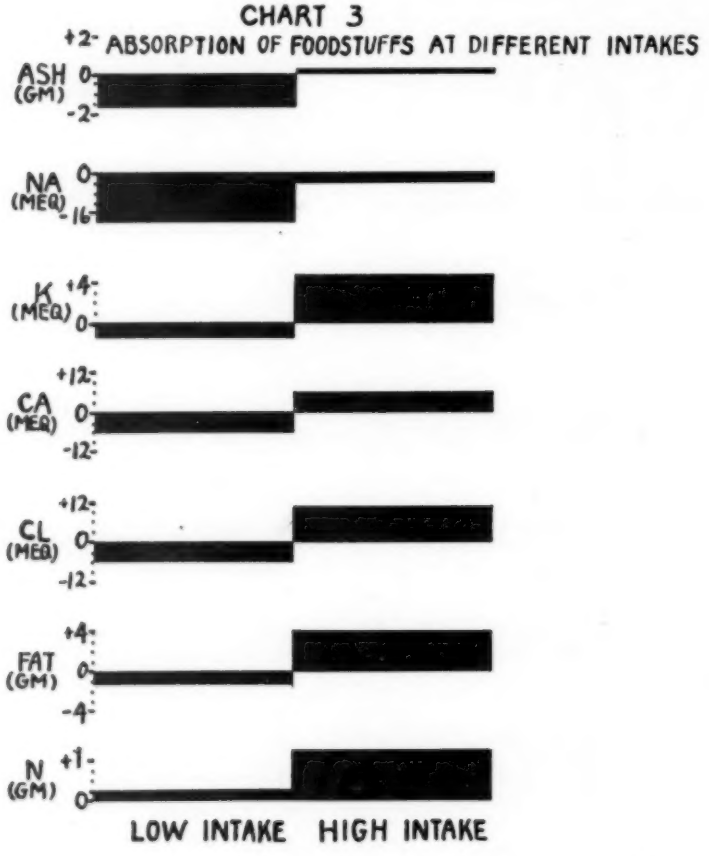
| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| Low Intake (45 cal./kg.) | Oral intake | 195 | 0.96 | 3.2 | 4.8 | 7.4 | 3.9 | 4.73 | 0.66 | 3.84 |
| | Urine | 20 | 0.12 | 0.4 | 4.7 | 0.1 | 5.5 | | 0.11 | |
| | Feces | 285 | 2.62 | 22.9 | 6.2 | 13.6 | 10.0 | 6.00 | 0.41 | |
| | Absorbed | −90 | −1.66 | −19.7 | −1.4 | −6.2 | −6.1 | −1.27 | +0.25 | |
| | % Intake absorbed | −46 | −173 | −620 | −31 | −87 | −157 | −27 | +38 | |
| High Intake (100 cal./kg.) | Total intake | 810* | 3.77* | 24.0* | 14.4 | 22.4 | 26.2* | 14.20 | 1.97 | 3.78 |
| | Urine | 58 | 0.49 | 1.3 | 3.1 | 0.7 | 10.9 | | 0.53 | |
| | Feces | 460 | 3.51 | 28.0 | 9.6 | 19.2 | 15.5 | 10.00 | 0.67 | |
| | Absorbed | +350 | +0.26 | −4.0 | +4.8 | +3.2 | +10.7 | +4.20 | +1.30 | |
| | % Intake absorbed | +50 | +7 | −16 | +33 | +15 | +41 | +30 | +66 | 3.58 |

*Represents addition of 100 c.c. of normal saline parenterally to oral intake.

TABLE IV. CASE 23

| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| High Intake (137 cal./kg.) | Oral intake | 645 | 4.32 | 14.3 | 21.3 | 33.7 | 15.9 | 21.30 | 2.96 | 3.60 |
| | Urine | 86 | 1.10 | 0.6 | 24.8 | 0.3 | 4.5 | | 1.08 | |
| | Feces | 230 | 3.03 | 13.4 | 8.6 | 31.0 | 12.2 | 10.90 | 1.18 | |
| | Absorbed | +415 | +1.29 | +0.9 | +12.7 | +2.7 | +3.7 | +10.40 | +1.78 | |
| | % Intake absorbed | +64 | +30 | +6 | +60 | +8 | +24 | +49 | +60 | |
| Moderate Intake (69 cal./kg.) | Oral intake | 585 | 2.16 | 7.2 | 10.7 | 16.9 | 7.9 | 10.65 | 1.48 | 3.54 |
| | Urine | 140 | 0.76 | 0.4 | 32.2 | 0.1 | 3.4 | | 0.45 | |
| | Feces | 233 | 1.82 | 8.7 | 6.0 | 14.4 | 10.7 | 3.18 | 0.55 | |
| | Absorbed | +352 | +0.34 | −1.5 | +4.7 | +2.5 | −2.8 | +7.47 | +0.93 | |
| | % Intake absorbed | +60 | +16 | −21 | +44 | +15 | −35 | +70 | +63 | 3.44 |

CASE 23.—D. T. was a 2-month-old white male who developed a mild diarrhea on the ward; this subsided only to return with marked severity, whereupon he was transferred to the metabolism ward. In order to answer the criticism that the diarrhea may have become less severe by the time the last period of full feedings was reached, the usual feeding procedure was reversed. For the first



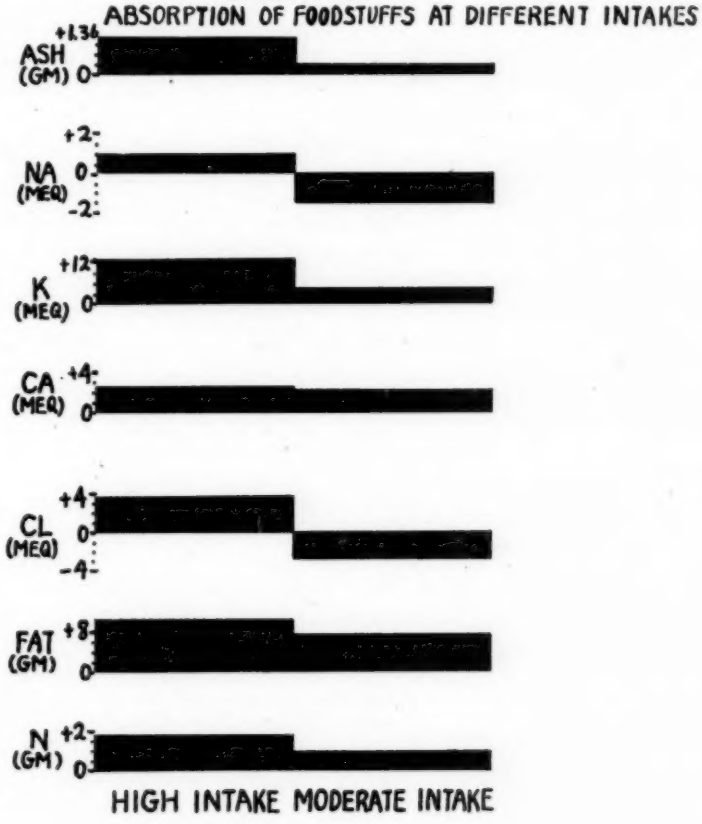

twenty-four hours a full calorie diet was given, while half the number of calories were offered for the second period. The data on Table IV and Chart 4 show that the higher intake caused better absorption regardless of the time offered. Five days after completion of the tests, while he was on 100 calories per kilogram his diarrhea stopped abruptly. At no time while under our observation were parenteral fluids needed.

CASE 27.—A. G. was a 7-week-old Puerto Rican boy who was admitted Jan. 19, 1947, as a boarder. Ten days later he developed capillary bronchitis and bilateral otitis media followed by severe diarrhea. He was treated with parenteral

electrolytes, dextrose, and whole blood, and complete oral starvation was instituted nineteen hours before transfer to the metabolism ward. He was still having as many as twenty watery stools daily at this time. It was decided to give the infant one period of full feeding followed by one of complete starvation (Table V). Supplementary 5 per cent dextrose solution was administered during both periods. The infant took a full diet well and had dextrose and normal saline as needed parenterally. Six days after his last test period the diarrhea ceased and recovery was uneventful.

CHART 4

ABSORPTION OF FOODSTUFFS AT DIFFERENT INTAKES




Case 28.—J. R. was a one-month-old white male infant who had received an exsanguination transfusion at birth because of erythroblastosis fetalis. He was doing well when he developed diarrhea on the ward. As in the previous patient, periods on full feedings and complete oral starvation were studied (Table VI). The fluid intake was augmented in each period by 150 c.c. of 5 per cent

TABLE V. CASE 27

| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| High Intake (106 cal./kg.) | Total intake | 835* | 3.84 | 12.7 | 18.9 | 30.0 | 14.2 | 18.90 | 2.62 | 4.14 |
| | Urine | 20 | 0.05 | 0.01 | 5.0 | 0.1 | 2.2 | | 0.11 | |
| | Feces | 361 | 3.06 | 18.5 | 7.2 | 18.0 | 14.9 | 6.03 | 0.65 | |
| | Absorbed | +474 | +0.78 | −5.8 | +11.7 | +12.0 | −0.7 | +12.87 | +1.97 | |
| | % Intake absorbed | +57 | +20 | −46 | +62 | +40 | −5 | +68 | +75 | |
| Oral Starvation | Total intake | 1055† | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3.96 |
| | Urine | 700 | 0.39 | 4.3 | 64.0 | 0.7 | 11.0 | | 0.79 | |
| | Feces | 178 | 1.43 | 6.7 | 5.7 | 5.8 | 8.2 | 2.22 | 0.30 | |
| | Absorbed | +877 | −1.43 | −6.7 | −5.7 | −5.8 | −8.2 | −2.22 | −0.30 | 3.78 |

*Represents addition of 250 c.c. of 5 per cent dextrose parenterally to oral intake.
†Represents addition of 950 c.c. of 5 per cent dextrose parenterally to oral intake.

TABLE VI. CASE 28

| | | WATER (C.C./DAY) | ASH (GM./DAY) | Na. (MEQ./DAY) | K. (MEQ./DAY) | Ca. (MEQ./DAY) | Cl. (MEQ./DAY) | FAT (GM./DAY) | N. (GM./DAY) | WT. (KG.) |
|---|---|---|---|---|---|---|---|---|---|---|
| High Intake (100 cal./kg.) | Total intake | 847* | 2.89 | 9.4 | 14.4 | 22.5 | 10.7 | 14.20 | 1.98 | 2.79 |
| | Urine | 370 | 1.55 | 15.4 | 17.0 | 1.2 | 24.4 | | 0.76 | |
| | Feces | 176 | 3.26 | 7.5 | 6.1 | 24.7 | 7.8 | 7.66 | 0.69 | |
| | Absorbed | +671 | −0.37 | +1.9 | +8.3 | −2.2 | +2.9 | +6.54 | +1.29 | |
| | % Intake absorbed | +79 | −13 | +20 | +57 | −10 | +27 | +46 | +65 | |
| Oral Starvation | Total intake | 653* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2.67 |
| | Urine | 460 | 0.34 | 1.2 | 10.2 | 0.5 | 5.3 | | 0.57 | |
| | Feces | 67 | 0.59 | 7.0 | 3.3 | 19.2 | 5.1 | 0.51 | 0.15 | |
| | Absorbed | +586 | −0.59 | −7.0 | −3.3 | −19.2 | −5.1 | −0.51 | −0.15 | 2.49 |

*Represents addition of 150 c.c. of parenteral 5 per cent dextrose in water to oral intake.

dextrose parenterally. The diarrhea improved slowly one week after he was placed on a 110 calories per kilogram diet, and he was discharged with occasional loose stools but with a consistent weight gain.

## COMMENT

The results are entirely consistent in the six cases presented in that increased absorption of all the food elements studied resulted from the higher food intake. A breakdown of the data into its individual food components follows.

*Water:* The volume of stool water serves as an index of the severity of the diarrheal process. Volumes over 200 c.c. per day, which were excreted by most of our patients, are indicative of severe diarrhea.[9] The smaller volumes observed in Case 26 are still significant as the infant weighed considerably less than the others in the series.

The conservation of water by the kidneys to compensate for the large fluid loss in the stools is demonstrated in almost all patients, but particularly in Cases 22 and 27, where a striking oliguria of 20 c.c. of urine per day was observed.

No effort was made to force water between feedings as it was important for our study that the measured amount of formula was taken without refusal or vomiting. Water deficits when present were made up by parenteral dextrose solution without electrolytes to prevent the complicating factor of parenteral absorption of minerals with subsequent excretion into the gut, which would invalidate the data on intestinal absorption. If it were not for the necessity of controlling conditions for the study it would certainly be more rational to combat the dehydration of diarrhea with a combination of dextrose and electrolyte solutions. The essentially similar trend in absorption observed in those subjects who received dextrose parenterally and those who did not would suggest the over-all validity of the procedure followed in the study.

*Ash:* In all cases, there was an increase in fecal ash when more food was given, but this increase was more than covered by the augmented intake resulting in higher absorption values. Thus the higher intake resulted in a net gain to the child.

*Sodium:* In all cases, the sodium output of the feces was large while the corresponding output in the urine was small, indicating marked conservation of the mineral on the part of the body. The loss of base, particularly sodium, from the stools in diarrhea is well known. That such losses are repaired considerably by feeding more is clearly shown by the data. Increasing the sodium intake either reduced the net loss of sodium or converted a negative balance of sodium into a positive one. The negative absorptions which remained in some patients even with full oral intakes, indicate the need of supplementary sodium either per os or parenterally.

*Potassium:* Potassium, too, is absorbed from the intestine in amounts roughly proportional to the amount offered. With the exception of Cases 22 and 26 on a low intake, positive absorptions resulted from even the smallest intakes. This would suggest wider use of the oral route for potassium administration.

*Calcium:* In the normal infant fed on cow's milk practically all of the calcium offered for excretion appears in the stool and amounts to roughly two-

thirds the intake.[9] In severe diarrhea as much as 90 per cent of the intake may be excreted in the stool, as is shown in our data. There was, however, a net gain in absorption as larger feedings were given in all the cases studied.

*Chloride:* A considerable amount of chloride is excreted by way of the stools in diarrhea. As is the case with sodium, this loss is appreciably repaired as more food containing chloride is given; however, a supplementary intake appears to be necessary in most instances.

*Fat:* Whereas the absorption of fat from the intestine of the normal infant amounts to 85 to 90 per cent of the intake, 60 per cent or less is absorbed in severe diarrhea.[9] Our data show levels of fat absorption varying from 27 to 72 per cent of the intake. The percentage absorption is not greatly affected by the quantity ingested, and it is therefore evident that a high food intake brings about a greater absolute amount of fat absorbed. This is particularly significant in view of the prevalent use of low fat formulas in the treatment of diarrhea, a regimen which may contribute to nutritional failure.

*Nitrogen:* In the normal infant, about 90 per cent of the nitrogen intake is absorbed. It was observed by Holt, and his associates[9] that loss of fecal nitrogen even in severe diarrhea is proportionally less than fat and that the percentage of nitrogen intake absorbed rarely falls below 75 per cent. We observed considerably lower values in some of our patients, the percentage absorption in one instance being as low as 27 per cent. As with the other components of the food, the larger intakes induced a larger absolute amount of nitrogen absorbed.

*Stools:* It is a common observation that the restriction of food causes diminution of the frequency and volume of stools in acute diarrhea. This coincides with our experience in these cases. If the frequency and volume of the stools were used as the criteria of successful therapy, one might well conclude that feeding exerted a deleterious effect on the diarrhea and that the more one starved the more successful was the treatment. I wish to point out again that it is the infant rather than the stools who should be the main concern, and the data herein presented have shown that the infant gains rather than loses with increased feedings even though this is accompanied by an increase in stool bulk. Case 27 illustrated this point very effectively. On a normal full diet twenty watery stools weighing a total of 383 Gm. were passed, in contrast to five watery stools weighing 186 Gm. when the infant was placed on complete oral starvation. From the metabolic data, however, it is evident that appreciable losses of mineral, fat, and nitrogen occurred when nothing was introduced by mouth, while substantial absorptions of all the food components except sodium and chloride took place when a full calorie diet was fed.

The comparison of these six infants on high and low food intakes indicates clearly that the more food that is given by mouth, the greater is the absolute loss of each food constituent in the stool. The stools are increased in volume and frequency as a result of the high feeding, which *apparently* causes an exacerbation of the diarrhea. It is equally clear, however, that the child absorbs more of each food ingredient as the food intake is increased. By that criterion he is better off, regardless of the appearance of the stools. Even in the severest diar-

rhea we observed no net loss of any food constituent due to washing-out of digestive secretions which had been stimulated by the increased food intake.

In regard to the clinical appearance of the infants, we cannot say with assurance that this was favorably affected during the short periods of liberal feeding. On the other hand, we observed no untoward changes in clinical appearance directly associated with the high feedings. We are inclined to think that longer periods of observation are needed on the two regimes in order to detect clinical differences.

These studies indicate clearly that effective intestinal absorption of all foodstuffs occurs even in the severest of diarrheas and that the absorption is roughly proportional to the intake. Unless it can be shown that a high intake is in some way deleterious or delays recovery (a matter that will be considered in the succeeding paper), it would seem desirable to feed such infants liberally and to disregard the appearance of the stools.

## SUMMARY

The absorption of nitrogen, fat, total ash, sodium, potassium, calcium, and chloride has been followed in six subjects with infantile diarrhea on normal and on reduced food intakes. It was found that absorption of each food ingredient was improved on the higher intakes, even though the fecal loss was increased.

From the point of view of absorption it would seem desirable not to restrict food in infantile diarrhea.

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# THE EFFECT OF EARLY ORAL FEEDING VERSUS EARLY ORAL STARVATION ON THE COURSE OF INFANTILE DIARRHEA

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IN THE preceding paper reasons were given for questioning the value of the time-honored procedure of early therapeutic starvation in cases of infantile diarrhea, and evidence was presented pointing to the value of early oral feeding. It was shown that even in very severe cases the retention of electrolytes, fat, and nitrogen was improved by feeding. There remained the question of the effect of early oral feeding on the course of the diarrhea. The limited amount of clinical material available at Bellevue Hospital would not permit a convincing answer on this point. We therefore sought an opportunity to study this question in some place where infantile diarrhea was prevalent and where a large controlled series of observations could be made on the duration of the disease in patients treated alternately by early therapeutic starvation and by early oral feeding.

Such an opportunity presented itself in the summer of 1947 through the courtesy of Dr. Ivan Hečko, who invited one of us (A. W. C.) to Bratislava to collaborate in a diarrhea study. The present report deals with a series of 115 patients of whom fifty-five were treated by the conventional regime of early oral starvation and sixty by full caloric feedings from the start.

The nature of the diarrhea which prevails in Bratislava every summer is not clearly established. Previous observations made by the University Bacteriological Institute had indicated that bacillary dysentery played a negligibly small part. This was confirmed during the period of the present study. Two and sometimes three stool cultures were made on all but four patients. In only four instances out of 111 were Shigella organisms recovered. Paracolon bacilli, *Proteus vulgaris*, and *Bacillus pyocyaneus* were occasionally isolated but apparently were of little etiological significance. A careful search for parenteral infection was made in every instance, but it was present in less than one third of the cases. It is possible that the unsanitary milk supply played a part in the etiology due to overgrowth of saprophytes, a factor thought to be responsible for "summer diarrhea" in the United States in years past. Raw cow's milk is in common use in Czechoslovakia. A virus etiology must also be considered, but this was not investigated.

## PROCEDURE

All patients with diarrhea were admitted to the ward. Alternate patients were offered full feedings from the start, the remainder being placed on a regime of oral starvation.

From the Department of Pediatrics, New York University, Dr. L. Emmett Holt, Director, and the University Children's Clinic, Bratislava, Czechoslovakia, Dr. Ivan Hečko, Director.

The expenses of this study were defrayed in part by grants from the John and Mary R. Markle Foundation and from American Relief for Czechoslovakia, in part by the Ministry of Health of Czechoslovakia.

The correction of shock, dehydration, and acidosis received immediate attention in all cases. Plasma (reconstituted from the dried state) was administered by intravenous push infusion in all cases of shock. Acute dehydration was repaired by a solution of equal parts of 10 per cent dextrose and physiologic saline. When clinical acidosis was present, a 5 per cent solution of sodium bicarbonate was added to the dextrose-saline mixture. The total amounts of the various fluids administered were dictated by clinical judgment rather than by laboratory data, as equipment for the latter was lacking. Ten per cent dextrose and 3 per cent Amigen containing electrolytes* were used intravenously to support nutrition in those infants who were not able to take food by mouth for prolonged periods.

After the initial parenteral fluid therapy, the patients placed on the therapeutic starvation regime received water by mouth for twenty-four to forty-eight hours, followed by small feedings of a formula composed of powdered milk, sugar, and water. The formulas were made up so that their concentrations were isocaloric with breast milk, with one-third of the total calories in the form of sugar. Analysis showed that with the exception of a somewhat lowered protein content the composition of the powdered whole milk used in this study was essentially the same as that used in the United States. Intake in the starved group began with amounts equivalent to 20 calories per kilogram of body weight and was increased at the rate of 20 calories per kilogram of body weight daily, or less frequently, depending on the nature of the stools. If, for example, the stools increased in frequency or became very loose, the formula was decreased by 20 or 40 calories per kilogram of body weight and increased slowly once again when the stools improved. Clinical evidence of dehydration was corrected with extra water by mouth or by parenteral saline and glucose.

The full feeding regime consisted of formulas made up of the same materials and concentrations as used in the starved group but in amounts equivalent to 80 calories per kilogram of body weight for infants over 6 months of age and 100 to 120 calories per kilogram for those under 6 months of age. The feedings were started as soon as possible after reparative parenteral therapy was under way, and were continued regardless of the nature and frequency of the stools until complete recovery took place. Only if the infant refused or vomited were feedings omitted and parenteral fluids substituted, but the infant was put on the same full feeding as soon as vomiting or refusal subsided. It was found that less than 10 per cent of the infants in the entire series refused or vomited once the initial state of dehydration, acidosis, and mineral loss was in some measure corrected. As in the starved group, water deficits not made up by the oral route were replaced parenterally. The principal differences between the two regimes lay not only in earlier feeding but feeding with full calories from the very onset. Chart 1 illustrates graphically these differences in intake. From the area between the two curves it may be computed that the fed group received 40.6 per cent more food during the first week than did the starved group.

*Supplied by the courtesy of Mead Johnson & Company, Evansville, Ind.

Sulfathiazole and penicillin were used in all cases where they were believed to be of value in treating complicating infections. Sulfaguanidine was given equally to the first fifty patients in both groups but not to the rest.*

One cubic centimeter of crude liver extract was given intramuscularly to all patients in both groups on admission.

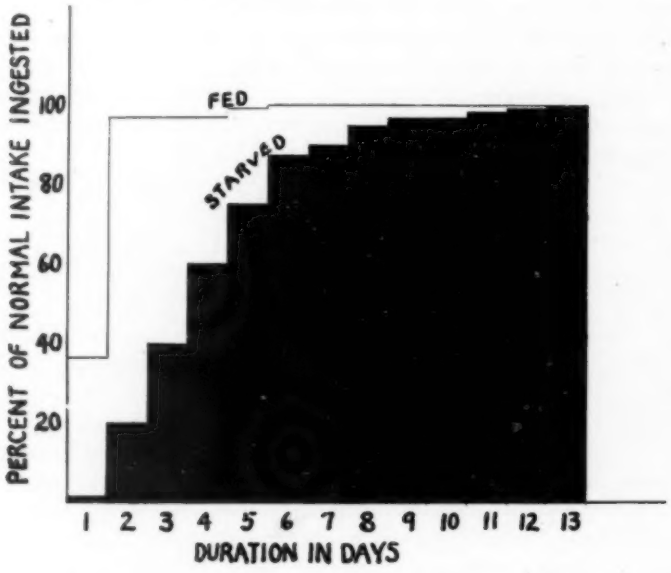


Chart 1.—Per cent of normal intake ingested per day in starved and fed groups. Normal intake: 100 calories per kilogram in infants under 6 months; 80 calories per kilogram in infants over 6 months.

Specimens from the first two stools (and often a third) were collected from the diaper and placed in freshly prepared tetrathionate enriching media and sent by messenger to the University Bacteriological Institute. The material was then incubated and plated on s.s. agar, from which colonies were identified by the usual accepted procedures.

## RESULTS

A total of 115 patients were observed in all. There were twelve fatalities, resulting in a mortality of 10.4 per cent. Two deaths were in infants who were taken out of the hospital without consent and were reported as having died at home. The remaining ten were all autopsied. Acute complications such as lateral sinus thrombosis and peritonitis resulted in two early deaths; however, the majority died after a long drawn-out course with malnutrition, complicating infection (particularly purulent otitis media), inanition, and finally terminal collapse. Autopsies on these patients, as expected, were not revealing. Although

*Evaluation of the efficacy of sulfaguanidine in the treatment was not possible because observations on alternate controls without drug were not made.

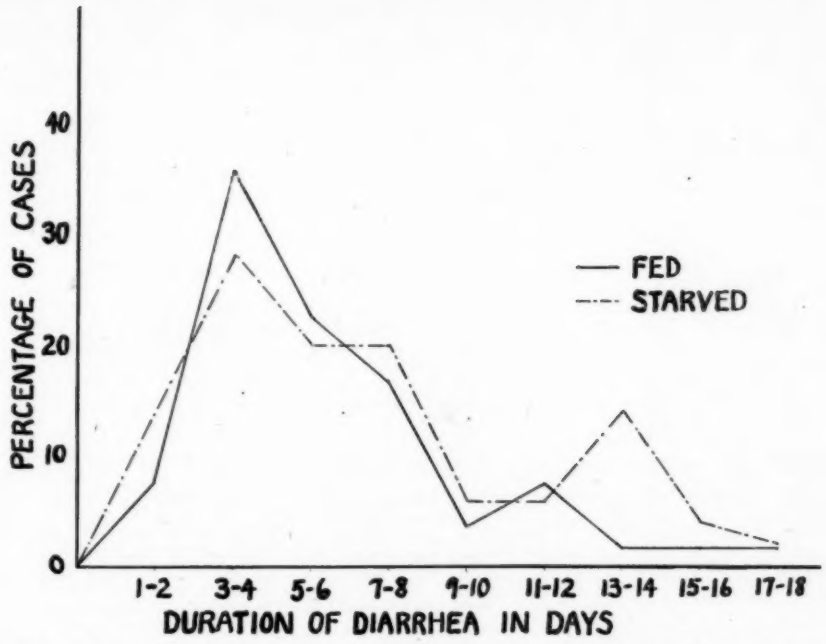


Chart 2.—Distribution curves showing duration of diarrhea with oral feeding and oral starvation.

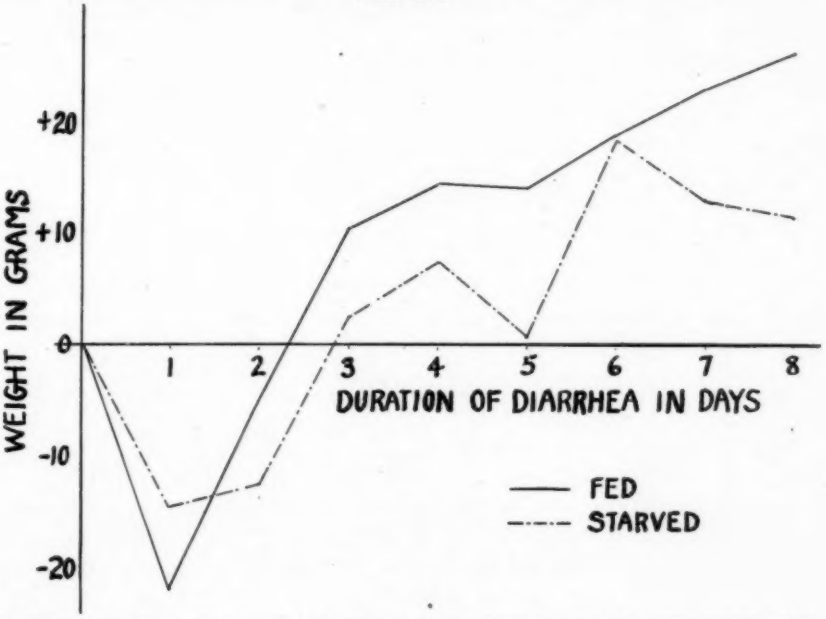


Chart 3.—Composite weight curves showing average algebraic sum of daily weight gains and losses.

TABLE I. ORAL STARVATION

| CASE | AGE (MO.) | INITIAL WT. (KG.) | DURATION OF DIARRHEA (DAYS) | STOOL CULTURE | COMMENT |
|---|---|---|---|---|---|
| 1 | 9 | 6.54 | 4 | Neg. for dysentery | Moderate dehydration |
| 4 | 8 | 4.62 | 8 | Neg. for dysentery; *P. vulgaris* | Premature; condition fair |
| 6 | 7 | 7.00 | 7 | Neg. for dysentery; *P. vulgaris* | Acidosis, shock, dehydration |
| 8 | 8 | 6.40 | 4 | Neg. for dysentery; *P. vulgaris* | General condition fair |
| 10 | 2 | 2.10 | 6 | Neg. for dysentery | Emaciation, marked dehydration |
| 12 | 23 | 7.00 | 7 | Neg. for dysentery | Emaciation, rickets |
| 14 | 4 | 3.84 | 11 | Neg. for dysentery; *P. vulgaris* | General condition fair |
| 18 | 13 | 8.00 | 5 | Neg. for dysentery | Malnutrition |
| 20 | 12 | 8.94 | 7 | Neg. for dysentery | General condition fair |
| 22 | 12 | 5.60 | 3 | Neg. for dysentery; *P. vulgaris* | Marked emaciation |
| 24 | 5 | 4.58 | 6 | Neg. for dysentery | Purulent otitis media *(Staph. aureus)* |
| 26 | 5 | 6.05 | 6 | Neg. for dysentery | Shock, dehydration, acidosis |
| 28 | 22 | 7.80 | 4 | Neg. for dysentery | Acidosis, dehydration |
| 30 | 4 | 4.39 | 4 | Neg. for dysentery | Malnutrition, dehydration |
| 32 | 2 | 4.30 | 4 | Neg. for dysentery | Severe dehydration |
| 34 | 2 | 3.55 | 8 | Neg. for dysentery | Severe shock, acidosis, dehydration |
| 36 | 7 | 5.35 | 6 | Neg. for dysentery | General condition good |
| 38 | 6 | 4.80 | 7 | Schmitz bacillus | Emaciation, dehydration |
| 39 | 12 | 5.20 | 13 | Neg. for dysentery | Purulent otitis media (pneumococci) |
| 40 | 11 | 5.70 | 7 | Neg. for dysentery | Emaciation, dehydration |
| 42 | 7 | 5.40 | 6 | Neg. for dysentery | Shock, severe dehydration |
| 42'* | 7 | 5.32 | 3 | Neg. for dysentery | Relapse due to otitis media |
| 46 | 16 | 8.80 | 13 | *Shigella flexneri* | General condition fair |
| 48 | 18 | 10.70 | 9 | Neg. for dysentery | Primary tuberculosis |
| 51 | 9 | 9.80 | 3 | Neg. for dysentery | General condition good |
| 53 | 8 | 6.10 | 16 | Neg. for dysentery | Relapse due to otitis media (pneumococci) |
| 59 | 2 | 4.21 | 14 | Neg. for dysentery | Relapse due to pharyngitis |
| 61 | 10 | 7.80 | 8 | Neg. for dysentery | General condition fair |
| 63 | 6 | 6.60 | 4 | Neg. for dysentery; *P. vulgaris* | General condition fair |
| 65 | 7 | 7.80 | 5 | Neg. for dysentery | General condition good |
| 67 | 6 | 7.25 | 5 | Neg. for dysentery | Pharyngitis, moderate dehydration |
| 69 | 6 | 4.00 | 10 | Neg. for dysentery | External otitis, dehydration |
| 71 | 9 | 7.80 | 4 | Neg. for dysentery | General condition fair |
| 73 | 9 | 5.25 | 5 | Neg. for dysentery | Emaciation, dehydration, purulent otitis media |
| 75 | 8 | 7.40 | 8 | Neg. for dysentery | Shock, severe dehydration |
| 77 | 7 | 6.40 | 3 | Neg. for dysentery | Shock, dehydration, otitis media |
| 79 | 3 | 4.36 | 11 | Neg. for dysentery | Acidosis, dehydration, otitis media (pyocyaneus) |
| 83 | 5 | 5.64 | 13 | Neg. for dysentery | Pyuria *(pyocyaneus)* |
| 85 | 9 | 7.00 | 7 | Neg. for dysentery | Pyuria *(B. coli)* |
| 87 | 4 | 4.90 | 3 | Neg. for dysentery | Shock, severe dehydration |
| 89 | 2 | 3.94 | 4 | No culture done | Shock, severe dehydration |
| 91 | 8 | 6.16 | 16 | Neg. for dysentery | Bronchopneumonia, otitis media |
| 93 | 12 | 6.70 | 5 | Neg. for dysentery | Severe dehydration |
| 95 | 12 | 7.50 | 10 | Neg. for dysentery | Acute bronchitis |

*The prime (') indicates patients who suffered a relapse of the diarrhea after at least one week's remission.

TABLE I—CONT'D

| CASE | AGE (MO.) | INITIAL WT. (KG.) | DURATION OF DIARRHEA (DAYS) | STOOL CULTURE | COMMENT |
|---|---|---|---|---|---|
| 97 | 12 | 6.52 | 18 | Neg. for dysentery | Otitis media, moderate dehydration |
| 99 | 2 | 4.00 | 4 | No culture done | Pyodermia, condition fair |
| 101 | 4 | 4.68 | 14 | Neg. for dysentery | Congenital syphilis |
| 105 | 5 | 6.80 | 14 | Neg. for dysentery | Purulent otitis media *(Staph. aureus)* |
| 107 | 4 | 4.40 | 14 | Neg. for dysentery | Shock, acidosis, dehydration, purulent cervical adenitis. |
| 109 | 4 | 3.80 | 11 | *Shigella flexneri* | Shock, acidosis, dehydration purulent otitis media (streptococci) |
| Average for total 50 cases | 7.9 | 5.97 | 7.8 | | |

seven deaths occurred in the fed group and five in the starved group, the series was too small to make deductions as to the relation of oral therapy to death. The clinical impression was that it played little if any role whatever.

Excluding the twelve fatalities, observations on fifty patients treated by oral starvation and fifty-three by oral feeding are tabulated (Tables I and II).

*A. Duration of Diarrhea.*—It was evident that certain criteria had to be set up to define the state of recovery from diarrhea to which both groups must adhere. These criteria were: (1) absence of diarrheal stools on a normal intake of food by mouth, and (2) gain in weight not dependent on parenteral fluids which persisted for at least one week. The minimum number of days after admission when both criteria were satisfied was regarded as the time required for recovery from diarrhea, i.e., the duration. Relapses were considered separate cases if they occurred after a full week's remission. These cases are represented in the table by a number accompanied by a prime (′). From the tables the average duration of diarrhea was 7.8 days for the fifty patients in the starved group and 6.1 days for the fifty-three patients in the fed group. The difference between the two figures is not statistically significant. Distribution curves showing duration of diarrhea with oral feeding and starvation are plotted in Chart 2.

*B. Weight Gains or Losses.*—Chart 3 shows composite weight curves for the two groups. The data were derived from the average algebraic sum of the daily weight gains or losses up to the eighth day of hospitalization. Discharges after the eighth day lowered the number of the original series in both groups so further data would not have been significant. Although the average drop in weight on the first day was slightly greater in the fed group, this group subsequently showed a progressive weight gain which was greater than in the starved group.

*C. Stools.*—Although the volume of stool was not measured, the clinical impression was that the stools of those in the fed group were much larger and contained more solid matter than those obtained from the starved group. This observation has been substantiated by measurements of stool volumes in the metabolic studies reported in the previous paper. As was pointed out there, the

TABLE II. ORAL FEEDING

| CASE | AGE (MO.) | INITIAL WT. (KG.) | DURATION OF DIARRHEA (DAYS) | STOOL CULTURE | COMMENT |
|---|---|---|---|---|---|
| 2 | 1 | 2.10 | 6 | Neg. for dysentery | Emaciation, dehydration |
| 3 | 8 | 4.50 | 7 | Neg. for dysentery; *P. vulgaris* | Premature; condition fair |
| 3'* | 8 | 4.50 | 12 | Neg. for dysentery; *P. vulgaris* | Relapse, cause? |
| 4' | 8 | 4.50 | 11 | Neg. for dysentery | Relapse due to pharyngitis (pneumococci, streptococci) |
| 5 | 8 | 4.50 | 7 | Neg. for dysentery | Congenital syphilis, malnutrition |
| 7 | 6 | 7.00 | 6 | Neg. for dysentery; Paracolon bacillus | Shock, severe dehydration |
| 9 | 12 | 5.90 | 6 | Neg. for dysentery | Severe malnutrition |
| 11 | 8 | 6.76 | 3 | Neg. for dysentery | Moderate dehydration |
| 13 | 14 | 7.90 | 6 | Neg. for dysentery; *P. vulgaris* | Severe dehydration |
| 15 | 3 | 3.95 | 3 | Neg. for dysentery; *B. pyocyaneus* | Harelip, moderate dehydration |
| 16 | 2 | 3.55 | 5 | Neg. for dysentery | Apathy, severe dehydration |
| 17 | 16 | 9.00 | 4 | Neg. for dysentery | General condition fair |
| 19 | 6 | 5.10 | 4 | Neg. for dysentery | General condition good |
| 21 | 4 | 5.10 | 8 | Neg. for dysentery | Mastoiditis (pneumococci), dehydration |
| 23 | 9 | 7.30 | 15 | Neg. for dysentery; *P. vulgaris* | Relapse due to otitis media |
| 25 | 7 | 5.30 | 4 | Neg. for dysentery; *P. vulgaris* | Otitis (streptococci) dehydration |
| 27 | 8 | 8.10 | 6 | Neg. for dysentery; *P. vulgaris* | Acidosis, dehydration; otitis media |
| 29 | 8 | 8.15 | 4 | Neg. for dysentery | General condition fair |
| 31 | 5 | 3.25 | 2 | Neg. for dysentery; *P. vulgaris* | Emaciation, dehydration |
| 33 | 2 | 3.90 | 2 | Neg. for dysentery | Malnutrition, dehydration |
| 35 | 4 | 3.10 | 3 | Neg. for dysentery | Emaciation, severe dehydration |
| 37 | 6 | 6.00 | 2 | Neg. for dysentery | General condition good |
| 40' | 11 | 5.88 | 7 | Neg. for dysentery | Relapse due to pharyngitis |
| 41 | 9 | 7.80 | 7 | Neg. for dysentery; *P. vulgaris* | Severe dehydration |
| 45 | 11 | 6.00 | 11 | Neg. for dysentery | Apathy, moderate dehydration |
| 47 | 10 | 7.60 | 3 | Neg. for dysentery | General condition fair |
| 50 | 2 | 3.55 | 6 | Neg. for dysentery | Emaciation, chronically ill |
| 52 | 5 | 4.65 | 8 | Neg. for dysentery; *B. pyocyaneus* | General condition fair |
| 54 | 10 | 5.60 | 4 | Neg. for dysentery | Bronchopneumonia; condition poor |
| 60 | 7 | 5.50 | 4 | Neg. for dysentery | Relapse at home, cause? |
| 64 | 5 | 3.90 | 6 | Neg. for dysentery | Acidosis, dehydration, cervical adenitis incised and drained. |
| 64' | 5 | 4.32 | 8 | Neg. for dysentery | Relapse due to inadequate drainage? |
| 66 | 5 | 5.43 | 4 | Neg. for dysentery | Pyuria *(B. coli)* |
| 70 | 12 | 9.00 | 2 | Neg. for dysentery | Shock, dehydration, acidosis, purulent otitis media (pneumococci) |
| 72 | 7 | 5.75 | 6 | Neg. for dysentery | Shock, severe dehydration |
| 74 | 5 | 4.30 | 4 | Neg. for dysentery | Malnutrition, rickets? |
| 76 | 7 | 5.30 | 12 | Neg. for dysentery | Shock, dehydration, otitis media abscess of thigh *(pyocyaneus)* |
| 78 | 1 | 2.70 | 3 | Neg. for dysentery | Shock, severe dehydration |
| 80 | 4 | 3.80 | 5 | Neg. for dysentery | Admitted in extremis, dehydrated; stormy course |

*The prime (') indicates patients who suffered a relapse of the diarrhea after at least one week's remission.

TABLE II—CONT'D

| CASE | AGE (MO.) | INITIAL WT. (KG.) | DURATION OF DIARRHEA (DAYS) | STOOL CULTURE | COMMENT |
|---|---|---|---|---|---|
| 80′ | 4 | 3.60 | 7 | Neg. for dysentery | Relapse due to too early discharge? |
| 82 | 5 | 6.90 | 18 | Neg. for dysentery | Severe dehydration bronchopneumonia, purulent otitis media *(pyocyaneus)* |
| 84 | 14 | 7.60 | 5 | Neg. for dysentery | Acidosis, severe dehydration |
| 86 | 5 | 5.00 | 7 | Neg. for dysentery | Moderate dehydration |
| 88 | 12 | 5.50 | 10 | Neg. for dysentery; *P. vulgaris* | Malnutrition, moderate dehydration |
| 90 | 5 | 6.04 | 4 | No culture done | Shock, severe dehydration |
| 94 | 10 | 8.00 | 3 | Neg. for dysentery | General condition fair |
| 96 | 15 | 8.40 | 3 | Neg. for dysentery | Lobar pneumonia, dehydration |
| 98 | 6 | 5.59 | 4 | Neg. for dysentery | Otitis media (streptococci), dehydration |
| 100 | 5 | 5.65 | 14 | No culture done | General condition fair |
| 102 | 3 | 3.14 | 3 | Neg. for dysentery | General condition fair |
| 104 | 8 | 9.00 | 3 | Neg. for dysentery | General condition fair |
| 106 | 24 | 6.20 | 10 | Neg. for dysentery | Otitis media (pneumococci), severe dehydration |
| 108 | 2 | 3.65 | 6 | Neg. for dysentery | Shock, severe dehydration |
| Average for total 53 cases | 7.3 | 5.56 | 6.1 | | |

increase in stool volume incident to feeding is not a contraindication to the giving of oral food; on the contrary, more food is absorbed when the infant is on an oral feeding regime despite the increased loss in the stools.

## COMMENT

The data presented indicate that early oral starvation, although it improves the appearance of the stools and decreases their frequency, fails to shorten the course of the diarrhea; actually the course in the starvation group was a trifle longer. The difference, however, does not appear to be statistically significant, and we are inclined to conclude that the duration of the digestive disturbance is conditioned by factors unrelated to the food. Since the traditional fear of prolonging digestive intolerance by oral feeding seems therefore to be an unwarranted one, there is every reason for taking advantage of the increased absorption of foodstuffs on a high food intake, which was demonstrated in the preceding paper. It would seem appropriate at this point to recall the statement made a quarter of a century ago by Park:[1] "The habit of starving an infant just because he has frequent stools is fallacious and gives rise to disastrous results. I have often thought in retrospect that many infants on our wards might have been fed more successfully if the stools had been totally disregarded."

In reaching the conclusion that the oral route should be used to the greatest extent in infantile diarrhea, we wish to emphasize that we are not urging it as a substitute for parenteral electrolyte or food administration. The gains which have resulted from the latter in recent years are far beyond the realm of dispute. Our point is that the best of parenteral therapy today has its shortcomings, and

for this reason the oral route should be employed as far as possible. By this means the patient's nutrition is best maintained, and it is to be hoped that some of the results of late nutritional failure can be avoided. In this respect an analogy between the treatment of diarrhea and that of typhoid fever may be drawn. The philosophy of supporting nutrition in the typhoid patient by a liberal, high caloric, low roughage diet was a radical departure from the accepted therapy when first introduced by Coleman[2] and Dubois,[3] but the clinical results of a generation have demonstrated the basic soundness of this approach.

Attention should be called to the limitations of early oral feeding. It is obviously impractical in the presence of vomiting. In the case of the acutely dehydrated infant who is being given infusions, the horizontal posture and difficulty in belching the baby necessitate caution in giving bottle feedings, for there is danger of regurgitation and aspiration. Under these circumstances, gavage may be employed with greater safety. It is our experience, however, that vomiting rarely causes difficulty once the infant is brought out of the stage of dehydration, shock, and acidosis.

## SUMMARY

Data have been presented on 115 patients with infantile diarrhea studied at the University Children's Clinic, Bratislava, Czechoslovakia. Of this group, twelve died, a mortality of 10.4 per cent. The remaining 103 patients were divided alternately into those fed full calories at the onset and those on therapeutic oral starvation. The duration of the diarrhea was not prolonged under the feeding regime. There was a more prompt and consistent weight gain in those who were fed, in spite of the larger volume of stool excreted.

The evidence presented by this clinical study substantiates the metabolic findings of the preceding paper that it is advantageous to feed the infant early with full calories in diarrhea rather than to follow the conventional treatment of oral starvation.

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# A SIMPLE FORMULA FOR PREMATURE AND FULL-TERM INFANTS

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MINNEAPOLIS, MINN.

THE need for a simple milk formula for babies is great. Such a formula would simplify not only the care of the baby at home, but it would do a great deal to remove the confusion that exists in the average hospital where many doctors prescribe individual formulas for their patients. Such confusion in the formula room breeds inefficiency and increases the chances for error error in preparation. Bacterial contamination is also much more likely under such circumstances.

Simple routines in patient and hospital care were a necessity at the U.S. Naval Hospital in San Diego because of the transitory and often inexperienced personnel as a result of war conditions. It was, therefore, thought that standardization and simplification of the milk formula used for babies and infants in the hospital would help a great deal in solving this problem.

## STUDY

The purpose of this paper is to report the use of the simplest formula possible—namely, equal parts of evaporated milk and water.* This formula was used for fifty-six consecutive premature and approximately 700 full-term infants at the U. S. Naval Hospital in San Diego, over a one-year period. No carbohydrate was added to the formula because it was thought that carbohydrate increases colic, and recent studies have shown that most carbohydrates are rachitogenic.[1] The milk was not diluted below whole milk concentrations because recent studies have shown that premature infants thrive better on a high protein formula. (Whole cow's milk has 3.5 per cent protein as compared with 1.5 per cent protein in human milk.[2])

In most instances the infants were fed nothing for the first twelve hours of life. During the next twelve hours they received 5 per cent glucose in distilled water. The mixture of equal parts of evaporated milk and water was begun on the second day of life and was given without change in most instances until the infant was 5 months of age. After 5 months most of the babies were put on plain cow's milk. All premature infants weighing less than 4½ pounds were routinely fed by gavage tube. In many instances infants weighing between 4½ and 5 pounds had to be gavage-fed also. These gavage feedings were maintained until the infants exhibited a strong sucking reflex, at which time a gradual introduction of bottle feedings was begun. The amount of formula given was determined primarily by the infant's ability to retain his feedings and roughly by 150 to 200 c.c. per kilogram of body weight per day divided into eight three-hour feedings. Two very small infants were fed every two hours.

Read before the San Diego County Medical Society, Dec. 9, 1947.

*This formula is similar to plain whole cow's milk except that it is sterile, homogenized, and in most instances is fortified with vitamin D.

Parenteral fluids were rarely used. In instances when a prominent anemia developed, blood was given intravenously in amounts of 20 c.c. per kilogram of body weight. Vitamin therapy was begun in the premature infants at 3 weeks of age; a water-soluble preparation containing A, $B_1$, $B_2$, C, and D was given. Iron was not used routinely, but when given, ferrous gluconate was used. Solid foods were instituted beginning about the second month of age in the larger premature infants and in all full-term infants. The usual order of introduction of solid foods was: cereal, vegetables, fruits, meat, and eggs. By 5 months of age, most infants were taking these foods well.

For several reasons, the premature infants seemed to be the best group in which to study the effect of this simple mixture in more detail, although the full-term infants were fed the same formula. First of all, the premature infants remained in the hospital for a longer period of time. This helped to eliminate the personal factor of an apprehensive mother who was willing to attribute every strange occurrence in the baby to the new formula. Secondly, the nursing care was more personal in the premature infant nursery, and as a result better records were kept as to the number and nature of the stools, the response of the baby to the formula, and the daily weight. Thirdly, it was felt that in all probability if the premature infants thrived on the formula the full-term infants would do likewise.

## RESULTS OF STUDY

We were able to use the simple mixture of equal parts of evaporated milk and water routinely in all premature infants beginning on the second day of life with surprising success. In not a single instance did we have to resort to a change in the formula in the premature infants because of intolerance to the mixture. One premature infant who was transferred from an outside hospital had twelve loose stools the first day on the formula. This infant was given glucose water during the next twenty-four hours and then the formula was started again. No more loose stools were noted in this infant, and he gained weight well.

Most of the infants tended to have slightly more formed stools than the average newborn infant on a standard formula. Constipation, however, was observed in only two infants, and it lasted for only one day; no change in the diet was required. The number of stools per day varied from one to eight, and the average was five stools per day. None of the infants displayed an intolerance to the amount of fat contained in the formula unless the number of stools could be considered abnormal.

As seen by the charted weights (Figs. 1-6), all fifty-six premature infants gained weight well on the formula. Several infants had no physiologic weight loss, and the majority had only a small weight loss. The average premature infant in this series regained his birth weight in twelve days and was discharged from the hospital in twenty-seven days.

By definition (all infants weighing less than 5½ pounds), there were actually seventy-five premature babies born during the period of this study.

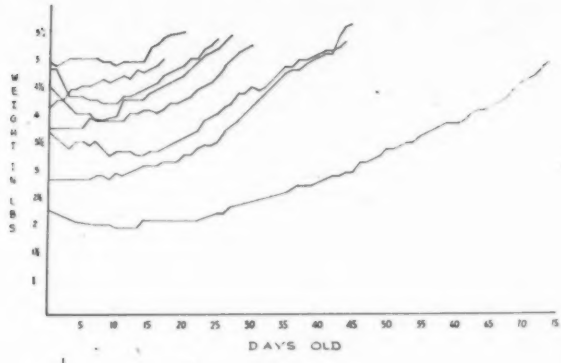



Fig. 1

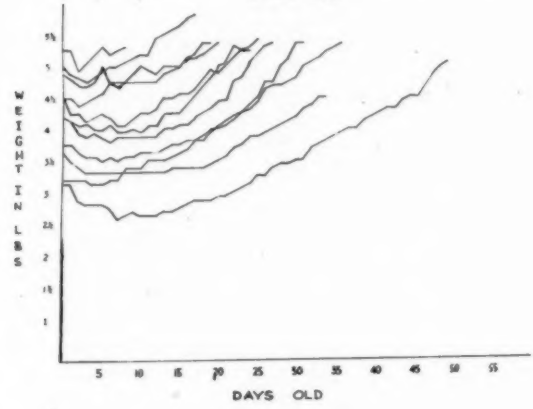



Fig. 2.

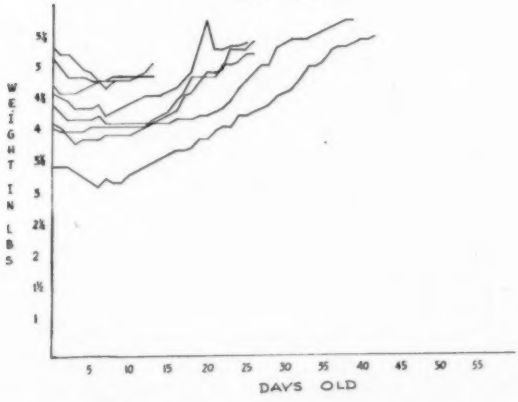



Fig. 3.

Figs. 1-3.—Graphs showing the daily weights of the fifty-six premature infants fed equal parts of evaporated milk and water.

Fig. 4.

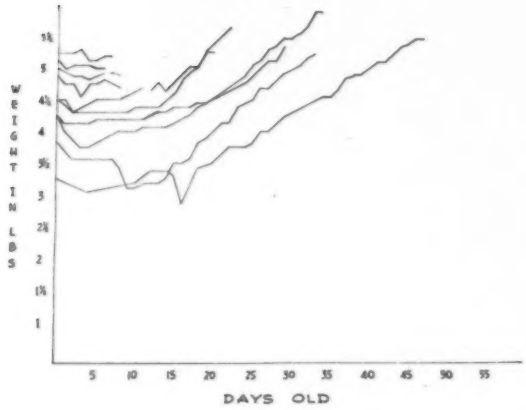



Fig. 5.

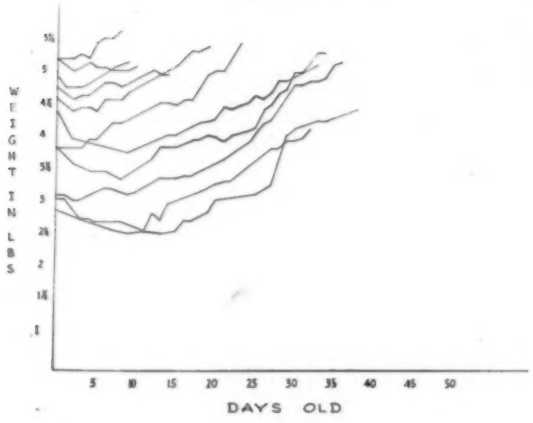
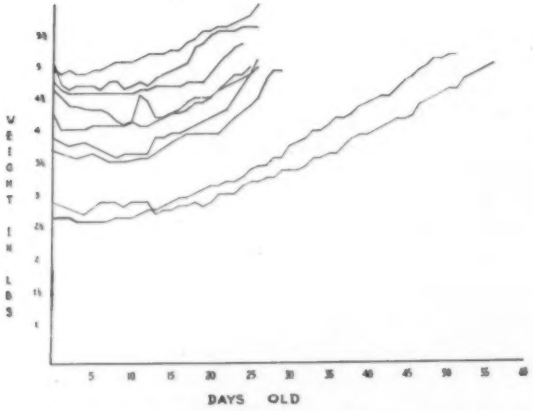



Fig. 6.




Figs. 4-6.—Graphs showing the daily weights of the fifty-six premature infants fed equal parts of evaporated milk and water.

Only fifty-six of these were admitted to the premature infant nursery. Ten of the remaining nineteen infants were large and mature enough to be placed in the regular nursery. The other nine babies died. Four of the deaths occurred in babies who were of only five to six months' gestation. Two of the other deaths were twins of six and one-half months' gestation. Two of the premature infants eventually developed an idiopathic hydrocephalus and were still alive at 9 months of age, when last seen. They did well on the formula, and I do not believe there was any association between the hydrocephalus and the diet.

As mentioned previously, this formula was also given to approximately 700 full-term infants, beginning on the second day of life until 5 months of age. Although many mothers were apprehensive and willing to attribute rashes, colic, constipation, and diarrhea to the new mixture, close appraisal revealed that the infants did well on the mixture. On an average, the weight at 6 months was 2 pounds above the median. Once the group psychology came into existence, most mothers welcomed the simple formula and recommended it to their friends. It was not long before the well baby clinic became a counselling center for discussion of the growth and development of infants rather than a diet center as it had previously been.

## DISCUSSION

The need for a standard simple formula both in the hospital and home was stressed earlier in this paper. This study, involving fifty-six premature infants and approximately 700 full-term infants, has shown that the simple mixture of equal parts of evaporated milk and water is well tolerated by infants from the second day of life to the fifth month of age. The babies gained weight consistently and did well in every respect.

McCulloch[3] and McMahon[4] have also used evaporated milk without added sugar in infant feeding for several years and feel that it is superior to mixtures with added carbohydrate. Both authors, however, favor changing the ratio of water to milk as the infant matures; I feel that such a change is not necessary in the majority of instances. McCulloch felt that evaporated milk without added sugar "is a suitable food for all normal infants and small children." He likewise suggested the advantage of simplicity in preparation of such a formula over a mixture containing added sugar.

Hess[5] states in the recent edition of Brennemann that "slower increases in weight may be expected of the artificially fed infant." Actually the premature infants in this study regained their birth weight one to five days earlier and were discharged from the hospital one to two days earlier than those in Hess' series, all of whom were fed breast milk. (See Tables I and II.) Other investigators have shown that slightly altered cow's milk is actually better than breast milk for premature infants.[2]

The artificial feeding used in these premature infants apparently did not increase the morbidity or mortality rate in this series as suggested by Hess.[5] The over-all mortality rate in this series was 12 per cent as compared with 27 per cent in Hess' series. One of the premature infants developed bilateral submaxillary gland abscesses, from which a pure strain of *Staphylococcus aureus*

TABLE I. AVERAGE LENGTH OF STAY IN HOSPITAL

| BIRTH WEIGHT (LBS. AND OZ.) | DAYS | DAYS (HESS) |
|---|---|---|
| 2 and 3 to 3 and 5 | 45.3 | 45.7 |
| 3 and 5 to 4 and 6 | 30.7 | 30.5 |
| 4 and 6 to 5 and 8 | 17.7 | 19.9 |

TABLE II. AVERAGE DAY ON WHICH BIRTH WEIGHT WAS REGAINED

| BIRTH WEIGHT (LBS. AND OZ.) | DAY | DAY (HESS) |
|---|---|---|
| 2 and 3 to 3 and 5 | 13.9 | 18.6 |
| 3 and 5 to 4 and 6 | 12.8 | 14.4 |
| 4 and 6 to 5 and 8 | 10.8 | 11.8 |

was recovered. The infection responded well to penicillin. Except for this one case, no other infections occurred in the premature infant nursery during the study.

This study has convinced me that nearly all premature infants will do well, providing they are constitutionally able to live, if they are given excellent nursing care alone.

## SUMMARY

1. There is a great need for a simple formula for infants.

2. The simple mixture of equal parts of evaporated milk and water was used from the second day of life in fifty-six consecutive premature and 700 full-term infants with good results.

3. The premature infants fed this simple formula regained their birth weight earlier and were discharged from the hospital earlier than those in a comparable series.

## ADDENDUM

It is significant that such low morbidity and mortality rates occurred in this study. During the period the observations were made, a serious epidemic of diarrhea of the newborn infant with a high mortality rate plagued Southern California. Thirty infants in our regular nursery became ill; however, none of the premature infants developed diarrhea.

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# PROSPECTS FOR PREVENTION OF CHRONIC BRONCHITIS AND BRONCHIECTASIS

## Rational Management of Bronchopulmonary Infections by Penicillin Aerosol Therapy

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THE common background of chronic bronchitis and bronchiectasis is, in the majority of cases, chronic nontuberculous bronchopulmonary infection. Although the pathogenesis of bronchiectasis is still a matter of controversy, it seems to be well established that dilatation of bronchi may originate from those same illnesses which frequently initiate chronic bronchitis. It appears reasonable, then, to base a discussion of possible prevention of chronic nontuberculous pulmonary disease on the etiological features common to simple chronic bronchitis and bronchiectasis. Pyogenic respiratory infection of a primary character as in tracheobronchitis, or when secondary to such virus diseases as measles or influenza, is an important factor in bronchial suppuration with subsequent bronchial obstruction and atelectasis. These changes, reversible in the beginning, may lead to chronic pulmonary disease with fibrosis, emphysema, and bronchiectasis[1-3] (Table I).

This type of respiratory illness is very common; its actual incidence can be estimated only if it is realized that conditions diagnosed and indexed as acute bronchitis, grippe, and pneumonia frequently are but exacerbations of a fundamentally chronic disease.

The economic loss due to chronic bronchitis and bronchiectasis is enormous, expressed in missed working days and millions of dollars spent for more or less effective therapeutics. The suffering of many patients affected by these illnesses is great. The irregular school attendance of children in whom the diseases are developing only foreshadows the semi- or complete invalidism of many of them in later years.

It is true that in recent years the previous complacency toward this type of pulmonary ailment has changed to a more active approach. Chemotherapy and antibiotics give temporary help in many cases of chronic bronchitis, and successful surgical intervention in patients with bronchiectasis restores health in an increasing number of cases.

Great as these advances are, they do not solve the urgent problem of preventing chronic bronchopulmonary infections. Although the belief that not much can be done to avoid bronchiectasis still seems to be deep-rooted, a prophylactic approach has for many years been considered by farsighted physicians.[1, 4-8] They realized that a rational therapy should be based upon knowledge of all etiological factors involved and upon proper therapy of the infectious process in its early stages.

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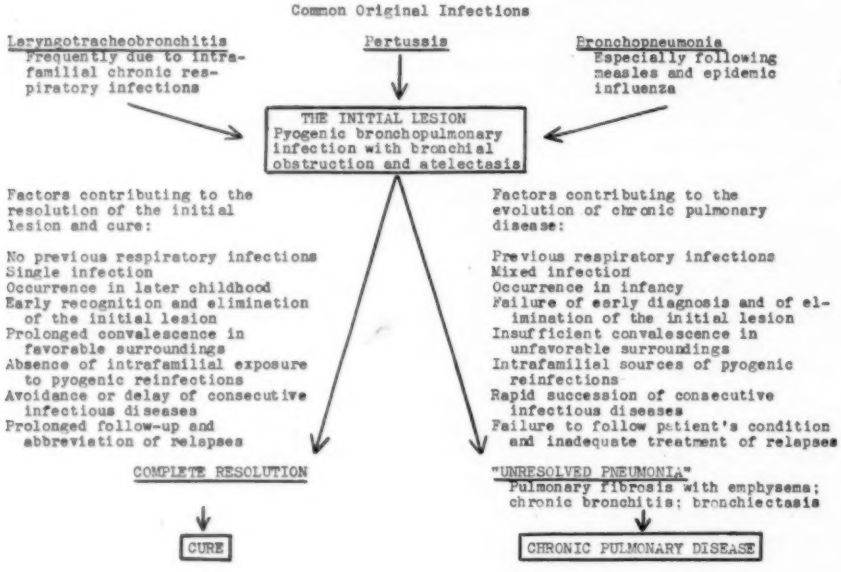
Most pleas for prevention of the chronic condition have been made by pediatricians or have been directed to them, since, in a high percentage of cases, chronic bronchitis with or without bronchiectasis has its onset in such common childhood diseases as bronchopneumonia (especially following measles) and pertussis.[5-12] Less appreciated, however, has been the significance of laryngotracheobronchitis as an initiator of pulmonary disease. This severe respiratory illness of early childhood, especially if complicated by bronchiolitis and bronchopneumonia, accounts not only for the death of a great many children, but also for the chronic illness of many more.

Table I: EVOLUTION OF BRONCHOPULMONARY INFECTION


Common Original Infections
Laryngotracheobronchitis
Frequently due to intrafamilial chronic respiratory infections
Pertussis
Bronchopneumonia
Especially following measles and epidemic influenza
THE INITIAL LESION
Pyogenic bronchopulmonary infection with bronchial obstruction and atelectasis
Factors contributing to the resolution of the initial lesion and cure:
No previous respiratory infections
Single infection
Occurrence in later childhood
Early recognition and elimination of the initial lesion
Prolonged convalescence in favorable surroundings
Absence of intrafamilial exposure to pyogenic reinfections
Avoidance or delay of consecutive infectious diseases
Prolonged follow-up and abbreviation of relapses
Factors contributing to the evolution of chronic pulmonary disease:
Previous respiratory infections
Mixed infection
Occurrence in infancy
Failure of early diagnosis and of elimination of the initial lesion
Insufficient convalescence in unfavorable surroundings
Intrafamilial sources of pyogenic reinfections
Rapid succession of consecutive infectious diseases
Failure to follow patient's condition and inadequate treatment of relapses
COMPLETE RESOLUTION
CURE
"UNRESOLVED PNEUMONIA"
Pulmonary fibrosis with emphysema; chronic bronchitis; bronchiectasis
CHRONIC PULMONARY DISEASE

Little attention is given to the most common source of recurrent laryngotracheobronchitis—namely, exposure of children to chronic nonspecific pulmonary infections in the family. Anxious as parents and physicians are to avoid any contact of children, especially of infants, with sufferers from banal acute respiratory infections, the danger for such children in being exposed daily to a relative affected by chronic respiratory illnesses other than tuberculosis, is still grossly disregarded. It is the rule rather than the exception to find chronic bronchitis of more or less severe character in one or more relatives of children affected by recurrent attacks of tracheobronchitis and pneumonia. In my experience, which confirms Duncan Leys' observations,[5] respiratory infections as initiators of chronic pulmonary disease in children under the age of 2, could be traced in at least 70 per cent of cases to conditions of the same type in the family. In this respect, it should be mentioned that, since

the end of World War II, an increasing number of small children have been exposed to pulmonary infections which have developed in members of their families. Many veterans were affected by epidemic respiratory infection while in service. Such illnesses are in many cases now proving of recurrent and even chronic character, thus constituting a continuous source of infection for their children.[13]

The significance of such pulmonary infections in early childhood is best demonstrated by the fact that among thirty-nine children over the age of 2 who had been hospitalized for acute bronchopneumonia, twenty-six had a definite history of recurrent respiratory episodes since infancy (Table II). This merely confirms the general experience that children whose respiratory organs are damaged in the early part of life usually react severely to consecutive infections involving the respiratory tract.

TABLE II. THE POTENTIALLY RECURRENT AND CHRONIC CHARACTER OF BRONCHOPNEUMONIA IN CHILDREN. A FOLLOW-UP ON FIFTY UNSELECTED PATIENTS, HOSPITALIZED FOR BRONCHOPNEUMONIA AND TREATED WITH SULFONAMIDES AND/OR PARENTERAL PENICILLIN

| AGE AT TIME OF HOSPITALIZATION | NO. OF CASES | CHILDREN'S CONDITION AFTER TWO YEARS | | |
|---|---|---|---|---|
| | | ILL HEALTH; PROGRESSIVE PULMONARY INFECTION | GOOD HEALTH BUT RECURRENT RESPIRATORY INFECTIONS | GOOD HEALTH; NO RECURRENT RESPIRATORY INFECTIONS |
| Under 2 years of age | 11 | 4 | 5 | 2 |
| 2-15 years of age with recurrent mild or severe respiratory infections since infancy | 26 | 9 | 14 | 3 |
| 2-15 years of age without recurrent respiratory infections | 13 | 3 | 5 | 5 |
| TOTAL | 50 | 16 | 24 | 10 |

It is true that many children may and do recover completely from pertussis, measles pneumonia, and laryngotracheobronchitis. A number of factors determine to a great extent whether an acute bronchopulmonary infection ends in cure or in chronic illness. Unfavorable factors include occurrence of the initial infection in infancy, subsequent pulmonary infections, lack of adequate treatment, and insufficient convalescence in poor and unhealthful surroundings. Favorable factors include the occurrence of measles pneumonia and pertussis in later childhood without preceding respiratory infections, and an undelayed, proper treatment with prolonged convalescence in a favorable milieu. A discussion of preventive measures against chronic bronchitis and bronchiectasis must take into consideration that only in a minority of cases can such favorable factors materialize. As in tuberculosis, a prophylactic approach should be dictated by the potential danger of the early lesion rather than by the possibility that the lesion may heal spontaneously.

Certain misconceptions regarding the evolution of chronic bronchopulmonary infection impede a rational management. In fact, there is hardly any other condition which is more frequently misinterpreted from the very beginning to its more advanced stages. A critical analysis of current treatments of the acute phase will indicate that by treating pyogenic tracheobronchitis and

bronchopneumonia like pneumococcal pneumonia, the illness is not always conquered. The primarily exudative process of pneumococcal pneumonia usually resolves completely. However, the suppurative process encountered in pyogenic bronchopulmonary infections is, as previously mentioned, an entirely different type of lesion. Short treatments with modern antibacterial substances prove highly effective in alleviating the acute infectious process, but do not regularly prevent a residual infection and continuation of some bronchial suppuration. Where free drainage from the involved bronchopulmonary segment is impaired, the restoration of a normal anatomical and physiologic state is inhibited.

In these instances, a variety of bronchial and peribronchial lesions, frequently labelled "unresolved pneumonia," mark the transition to chronic pulmonary disease. Bronchoscopic examinations[1] and x-ray findings such as mottling of the lungs or atelectasis, indicate that the underlying processes are others than true pneumonic consolidations. The slow disappearance of the lesions paralleled by persistent localized râles in the affected area is sufficient warning that the patient has not actually overcome his illness. The recent tendency to label such pulmonary conditions "atypical pneumonia" or "virus pneumonia" merely because they do not present the features of pneumococcal pneumonia or because they have been initiated by virus diseases, further deflects attention from their potentially chronic character. The consequences of neglecting to follow up these children generally become evident only after many years, when frank bronchiectasis is found at the site of the original infection, or chronic emphysema and pulmonary fibrosis have developed. Occasional observations on the condition of children after their apparent recovery from bronchopneumonia prove that a considerable number of them bear the mark of chronic pulmonary disease after a relatively short period.[5] Most alarming is the fact that current treatments of bronchopneumonia do not seem to have appreciably changed the situation Leys reported twenty years ago.

Out of fifty children hospitalized in 1945 for bronchopneumonia and treated with sulfonamides and/or penicillin, sixteen presented symptoms and frequently definite signs of subacute or chronic bronchopulmonary infection two years later. About half of these sixteen children had sought medical advice during these two years or had been rehospitalized for more severe relapses, some of them for another attack of bronchopneumonia. Twenty-four others of the fifty children, although apparently in good health, had been affected since their hospitalization in 1945 by relatively mild but recurrent respiratory episodes diagnosed as grippe, cold, and the like. Thus, only ten children of the whole group had remained free from respiratory symptoms during the two years following their bronchopneumonia. (Table II.)

A more detailed analysis of the fifty cases revealed the following: Thirty-nine children were over 2 years old at the time of their hospitalization; in twenty-one of these older children, the bronchopneumonia apparently was of the "primary type"; in the remaining eighteen, it was preceded by measles or pertussis. However, in twenty-six of these thirty-nine cases, the history revealed recurrent respiratory episodes, frequently of severe character, since early childhood. It seemed, moreover, that in cases of measles pneumonia and pertussis,

the tendency of the infection to become chronic was more pronounced in a child with previous respiratory infections.

Although these observations concern only a relatively small group, in which, moreover, other variables have not been considered, they indicate the potentially recurrent and chronic character of a condition generally misinterpreted as an acute illness. It also appears that current short treatments with modern antibacterial substances are not the solution. The situation parallels observations on the recurrence of other infections following treatments with sulfonamides and antibodies which frequently mask rather than prevent the development of a chronic condition.

As the bronchopulmonary infection takes its course, sometimes progressing rapidly but more often rather insidiously, proper management, which still could prevent irreparable damage, is frequently delayed by failure to realize the actual character of the disease and by futile therapeutic measures. The relatively good general health of the children and the lack of typical abnormal signs in between the characteristic exacerbations mislead parents and physicians alike. Coughing spells at night or in the morning are at first given scarcely any attention, or it is believed that the child might outgrow the tendency to "colds" or "croup." When, despite use of all available remedies, respiratory symptoms increase, and especially if the parents happen to notice such ominous symptoms as blood-streaked sputum, a chest x-ray is usually taken. In most instances the report "negative for tuberculosis" or "findings indicative of repeated upper respiratory infections" all too often gives the false assurance that no serious condition exists. Fortunately, the fruitless practice of placing children with bronchopulmonary infection in sanatoriums as potentially tubercular has been more and more discarded. Many doctors, however, still concentrate on ruling out tuberculosis, thereby losing sight of other serious pulmonary conditions which, more than tuberculosis, are likely to develop after measles, pertussis, and tracheobronchitis.

Equally grave consequences may result from erroneous evaluation of associated conditions and disguising symptoms as the cause of the disease. Kaiser's observations[14] on tonsillectomized and adenoidectomized children, compared with children not submitted to such surgical intervention, have revealed clearly that the removal of the supposed "focus of infection" in the upper respiratory system actually did not prevent the recurrence of bronchitis and pneumonia. Although a more conservative approach to tonsil and adenoid removal can be noted at present, it is still the exception rather than the rule to find children with chronic bronchitis who have not undergone such intervention. In all the discussions about upper respiratory infection as a cause of chronic pulmonary disease, and vice versa, the following fact has been insufficiently considered. Measles, pertussis, influenza, and other illnesses known to initiate chronic pulmonary infections frequently involve upper and lower respiratory systems simultaneously and leave their mark in both. Therefore it can not be expected that even successful elimination of nose, throat, or sinus infections can prevent the chronicity of an existing infectious process in the bronchopulmonary system.

The observations of Kaiser and Perry and King,[11] as well as the clinical history of many children seen in the office or clinic, indicate that chronic infection of the lower respiratory system is not infrequently initiated or aggravated by tonsillectomy and adenoidectomy. Therefore, it is imperative that the pediatrician, before giving his consent to these surgical measures, consider all factors possibly responsible for the child's symptoms, especially if the history indicates that such symptoms followed an infection of the lower respiratory tract.

The similarity of asthmatic symptoms in bronchial infections to true allergic asthma is another cause of misinterpretation and delayed rational treatment. Ever since earlier students of asthma emphasized the importance of proper distinction of "organic asthma" from "spasmodic asthma," the differential diagnosis between chronic bronchitis and true allergic asthma has been recognized as an important problem,[15] although it has been the subject of much controversy. In another paper,[16] I have stressed anew the significance of chronic bronchitis as the direct cause of what is variously diagnosed as asthmatic bronchitis, intrinsic asthma, bacterial and infectious asthma. The life history of children with asthma of this type usually indicates that asthmatic manifestations appeared in the course of a developing respiratory infection.[16-19] Such infection generally proves to have been initiated by acute respiratory episodes such as pneumonia, pertussis, or tracheobronchitis, rather than by previous respiratory allergy.[16] Attacks of wheezy dyspnea occurring in these instances can be sufficiently explained by bronchial obstruction due to infectious exudations. The prevalent conception that true allergy usually precedes or follows infectious asthma is not sufficiently substantiated by actual observations. An allergic condition, if found in children with bronchopulmonary infection, may complicate the picture, and if not properly treated, may aggravate the illness as would any other coexisting affection. However, the occurrence of so-called mixed atopic and infectious asthma does not necessarily imply that allergic mechanisms, per se, are responsible for irreversible lesions, which can be found in both allergic and nonallergic persons. Indeed, clinical observations on the etiology of bronchiectasis do not support the assumption of allergy as an appreciable etiological factor of this condition.[11, 12, 20-22] With regard to proper therapy, it is of secondary importance whether or not one accepts a hypothetical bacterial allergy as responsible for pulmonary infection. Attempts to desensitize a patient to bacterial agents, instead of attacking the invaders directly, are in our day no more rational than was tuberculin therapy for tuberculosis years ago. Nonspecific therapy, especially antibiotics, directed against the infection as such, is now widely applied in chronic asthma with infectious "complications." It is obvious that such treatment would bring more help to the patient if applied before the advanced stage had developed, regardless of whether or not allergy is found or suspected.

From what has been outlined thus far, it appears that a broad approach to the problem of prevention of chronic bronchopulmonary infection is a prerequisite for its possible solution. However, the principal goal remains the

earliest possible eradication of the infectious process. In searching for such therapy, I have found that continuous administration of penicillin at the site of infection by way of inhalation can accomplish more than any other treatment thus far known. Promising results with penicillin aerosol therapy in far-advanced pulmonary infection, initiated the first attempts three years ago to use this method in potentially chronic respiratory infections.[26]

It is not intended to elaborate in this paper on technical problems of penicillin aerosol therapy, which has been described in numerous publications.[23-25] Nevertheless, certain adaptations should be mentioned which are important in using this method for children with subacute and chronic bronchopulmonary infection. In these stages of the disease a treatment for several weeks or even months is required. Therefore, a method of giving penicillin aerosol at home in an efficient way and involving the least possible expense is essential.[27]

Nebulization by hand bulb is too cumbersome for treatment of any length, and oxygen as the source of pressure too expensive for many patients. A simple bicycle pump proves serviceable for the purpose if a glass-fiber filter is inserted between pump and nebulizer.[28] Such a pump can also be used by relatives of young children to fill a head tent, under which the patient breathes in the penicillin. The nebulizers used for aerolization of the antibiotic are the same as usually recommended for adults. The DeVilbiss No. 40 and Premo are efficient in most cases and are within the means of even patients of the lower income group. The Vaponefrin plastic nebulizer has proved especially helpful for children, both because it is unbreakable and because it reduces the nebulization period. Since it was found that many children preferred to inhale through the nose and exhale through the mouth, rather than vice versa, this mode has, in an increasing number of cases, been applied, using a nasal adapter. The rebreathing bag filled with hot water, recommended by Barach as an accessory, was found to complicate the treatment and was unnecessary in the majority of cases. It was used only if the addition of hot moisture was indicated or if the child lost a considerable amount of penicillin by improper breathing technique when inhaling directly from the nebulizer.

As for the required dosage of penicillin, high doses given at the start of treatment proved most effective in eliminating the active infection. One hundred thousand units of crystalline penicillin as supplied in vials or soluble tablets, administered two or three times daily, frequently accomplished the disappearance of respiratory symptoms within one or two weeks unless the condition was advanced. When the head tent was used, higher dosage was needed to allow for the unavoidable loss of penicillin involved in that method. In mild cases, it was found that one daily inhalation of 50,000 units of penicillin was sufficient to control the infection once it had subsided. In more severe cases, especially in those of long duration, high daily doses had to be continued for several months to assure a more stabilized condition. Since no clinical, roentgenologic, or laboratory methods reliably indicate the actual arrest of a bronchopulmonary infection, the treatment was discontinued only gradually and resumed immediately if respiratory symptoms reappeared.

The still-prevalent fear that prolonged administration of penicillin might produce serious untoward side-effects and might develop penicillin-resistance in the patient, did not seem to be substantiated in this series. Irritation of tongue and pharynx and skin reactions were observed in a number of patients, but were seldom of such severe character as to force discontinuing of the treatment. Rinsing of the mouth and antihistaminic drugs proved most helpful in counteracting side effects. A less prompt response to the antibiotic could in almost all patients be explained by the more serious character of the disease, improper treatment technique, and the like. In none of the patients from whom sputum could be obtained were pathogenic organisms found other than penicillin-sensitive ones. In the remaining patients, a prompt response to high doses of the antibiotic was held sufficient clinical evidence that pyogenic bacteria, such as are commonly found in bronchopulmonary infections, had been the causative agents. No efforts were made to obtain blood levels of penicillin, since high concentration of the antibiotic at the site of infection and not in the blood is the major aim of penicillin aerosol therapy.

An analysis of therapeutic effects of this new method should consider its lasting results rather than merely early responses, spectacular as the latter usually are. Therefore, the tabulation of treated patients includes only children who had been followed up for at least one year. Moreover, the tabulated cases were restricted to children who had been ill for at least three months, and had been previously treated by various other methods without appreciable improvement. Children with acute bronchitis, which usually cleared up after a few treatments, do not appear in this group. Neither do cases of frank bronchiectasis, because the evaluation of penicillin aerosol in such conditions is beyond the scope of this paper. Thus, only fifteen children, out of some 400 patients of all ages who had been treated with penicillin aerosol, were considered relevant material for this analysis.

Tuberculosis and other serious illnesses being ruled out, the diagnosis of subacute or chronic bronchopulmonary infection was based on a history of recurrent respiratory episodes following measles pneumonia, whooping cough, tracheobronchitis, etc. The most characteristic symptom was persistent cough. The absence of abnormal clinical, roentgenologic, and laboratory findings was not considered as ruling out the diagnosis of bronchopulmonary infection. Bronchographic studies were done in eight patients with severe infection, in whom bronchiectasis seemed most likely.

The three following case reports and the tabulation of the fifteen cases (Table III) may demonstrate the various problems involved in children suffering from bronchopulmonary infection. They also may reveal the potentialities as well as the limitations of penicillin aerosol as a therapy.

### CASE REPORTS

CASE 1.—The patient was an 11-year-old boy, first seen April 8, 1946. The mother suffered from bronchiectasis. The child previously was in good health except for minor respiratory episodes. He had had measles three months prior to examination, followed by persistent fever and cough. Sulfadiazine was given for four days, the symptoms subsided,

and the child was considered recovered after two more weeks. However, a productive cough continued. Physical and roentgenologic examination revealed unresolved bronchopneumonia in the left lower base. Penicillin aerosol therapy was administered for two months. The respiratory symptoms cleared up in ten days; the clinical and roentgenologic signs disappeared after one month. Treatment was continued for one more month. The patient remained in perfect health for eleven months after termination of treatment. In June, 1947, a mild productive cough reappeared without any abnormal clinical or roentgenologic findings. A second course of penicillin was given for three weeks with prompt response; there has been no recurrence of respiratory symptoms since then. The last recheck was on Jan. 15, 1948.

CASE 2.—The patient was an 8-year-old girl, first seen Oct. 18, 1945. There was no history of chronic respiratory diseases in the family. The child had no respiratory infections up to the age of 4. At that time she contracted pertussis, followed by mild but persistent cough. During each winter there were two to three febrile exacerbations. In October, 1944, she had pneumonia, treated at home with sulfonamides. The child was absent from school for six weeks due to poor general health and continuous cough. The condition improved during the following summer; however, with the beginning of fall, symptoms became worse again and the child had to stay home for another three weeks. There were no abnormal clinical or roentgenologic findings at the time of examination; she was in good general condition. Eight weeks of penicillin aerosol therapy eliminated all symptoms. There has been no relapse now for more than two years; the child has remained in perfect health.

CASE 3.—The patient was a 12-year-old girl first seen April 6, 1946. The father suffered from chronic bronchitis. Since the age of 10 months, the child had been affected by recurrent febrile respiratory episodes of persistent character. She had measles and pneumonia when 16 months old, followed by relapsing bronchitis. Tonsillectomy was performed at the age of 4, followed by aggravation of the condition. During the same year, she had pertussis. Antrum puncture was performed because of increasing respiratory symptoms. There were many hospital admissions, during which the condition was variously diagnosed. At the age of 5, asthmatic symptoms developed, and, since hay fever appeared in the picture, the condition was considered to be bronchial asthma. Skin tests were essentially negative, but allergy to house dust and bacterial allergy were suspected. In spite of allergic management, the cough with purulent, at times blood-streaked, sputum increased in severity. Tuberculosis had been ruled out by several examinations. After entering school, the child was often absent for a prolonged period. Essential findings were: poor general condition; marked dyspnea, even at rest; vital capacity 0.8 L.; wheezy and sonorous râles throughout both lungs; fluoroscopy and x-ray of chest essentially negative except for restricted motion of diaphragm with breathing and increased bronchovascular markings. Bronchographic studies did not reveal demonstrable bronchiectasis. The sputum was mucopurulent, negative for acid-fast bacteria; cultures revealed the prevalence of hemolytic streptococcus and *Staphylococcus aureus*.

The course under penicillin aerosol treatment was as follows: remarkable improvement of symptoms during the first week; after two months of treatment, hardly any cough, but still some wheezy dyspnea, especially on exertion. The general condition also improved considerably; the child gained 12 pounds in this period. During the first year of treatment, two minor relapses occurred when penicillin aerosol was discontinued tentatively, but they were controlled almost immediately by resumption of the treatment. At the end of the first year the condition seemed to be stabilized; the child had gained 28 pounds; the vital capacity had increased to 1.5 L.; the only remaining symptom was dyspnea, mostly on exertion, occasionally of asthmatic type. After the child had been in good health for several months without penicillin aerosol, a major relapse occurred in November, 1947, probably due to reinfection from her sister, who suffered from tonsillitis at that time. The relapse was characterized by high fever, asthmatic dyspnea, and severe cough with purulent, bloody sputum. Clinical and x-ray findings revealed atelectasis of the right middle lobe. The

TABLE III. OBSERVATIONS ON FIFTEEN CHILDREN WITH SUBACUTE AND CHRONIC BRONCHOPULMONARY INFECTION, TREATED WITH PENICILLIN AEROSOL

| CASE NO. | AGE AT ONSET OF ILLNESS | AGE AT START OF TREATMENT | DURATION OF ILLNESS | EXPOSURE TO FAMILIAL INFECTION | ORIGINAL AND CONSECUTIVE RESPIRATORY INFECTIONS | CONDITION AT START OF TREATMENT | PERIOD OF OBSERVATION | RESULTS OF TREATMENT |
|---|---|---|---|---|---|---|---|---|
| 1 | 11¾ yr. | 12 yr. | 3 mo. | Mother, bronchiectasis | *Measles pneumonia* | Acutely ill; unresolved bronchopneumonia | 18 mo. | Complete recovery after 2 mo. treatment; one mild relapse |
| 2 | 4 yr. | 8 yr. | 4 yr. | None | *Pertussis* at 4 yr.; pneumonia at 7 yr. | General health fair; no abnormal findings; persistent respiratory symptoms | 2½ yr. | Complete disappearance of symptoms after 2 mo. treatment; no recurrence; in excellent health |
| 3 | 5 yr. | 5½ yr. | 3 mo. | None | *Tracheobronchitis* following (?) measles; several relapses | Good general health; persistent respiratory symptoms | 1 yr. | Prompt response to treatment of 2 mo. duration; no recurrence |
| 4 | 5½ yr. | 6 yr. | 6 mo. | Mother, bronchiectasis | *Pertussis* | Good general health; persistent tracheobronchitis | 16 mo. | Prompt response to treatment of 2 mo. duration; one mild relapse |
| 5 | 6 mo. | 3½ yr. | 3 yr. | Father, chronic bronchitis; one sister, recurrent bronchitis | *Laryngotracheobronchitis* at 6 mo.; repeated relapses | Fair; localized bronchitis | 1 yr. | Completely recovered after 2 mo. treatment; no recurrence |
| 6 | 4 yr. | 15 yr. | 11 yr. | None | *Pertussis* at 4; repeated pneumonias | Severely ill; emaciated; extreme dyspnea | 2 yr. | Greatly improved under several courses of treatment; gained 26 lb.; is working regularly; at times mild respiratory symptoms |
| 7 | 5 yr. | 9 yr. | 4 yr. | Father, recurrent bronchitis | *Pertussis* at 5 | Good general condition, except persistent respiratory symptoms; no abnormal findings | 15 mo. | Prompt response to treatment of 2 mo. duration; one mild relapse |
| 8 | 2 yr. | 7 yr. | 5 yr. | None | *Laryngotracheobronchitis* at 2; measles at 6; several exacerbations | Good general condition; severe respiratory symptoms; emphysema | 15 mo. | Greatly improved; mild relapses controlled by resumption of treatment |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 9 | 6 mo. | 3½ yr. | 3 yr. | Father, chronic bronchitis; bronchiectasis (?) | *Laryngotracheobronchitis* at 6 mo.; 3 times bronchopneumonia | Good general condition; persistent respiratory symptoms; basal pathology left base; bronchopneumonia (?) | 13 mo. | Prompt response to treatment of 2 mo. duration; one relapse after scarlet fever; basal pathology cleared up |
| 10 | 6 mo. | 11 yr. | 10½ yr. | None | *Pertussis* at 6 mo.; measles pneumonia at 11 yr. | Unresolved measles, pneumonia; acutely ill; emaciated | 20 mo. | Completely recovered after 5 mo. treatment; one mild relapse; now in excellent health; gained 22 lb. |
| 11 | 1 yr. | 12 yr. | 11 yr. | Father, chronic bronchitis | *Laryngotracheobronchitis* at 1 yr.; pertussis at 5; measles, pneumonia at 7 | Severely ill; emaciated; diffuse bronchitis; emphysema, pulm. fibrosis | 1½ yr. | Good results; symptoms greatly reduced; gained 35 lb.; condition apt to recur if treatment discontinued |
| 12 | 2 yr. | 13 yr. | 11 yr. | None | *Laryngotracheobronchitis* at 2; measles at 10; bronchopneumonia at 12 | Poor general condition; severe respiratory symptoms; emphysema mild pulm. fibrosis | 2 yr. | Prompt response to treatment of 4 mo. duration; one severe and one mild relapse; now in good health; gained 23 lb. |
| 13 | 2 yr. | 11 yr. | 9 yr. | None | *Pneumonia* at 2; measles at 5; pneumonia (?) at 10 | Poor general condition; diffuse bronchitis; emphysema | 2½ yr. | Greatly improved after 6 mo. treatment; one mild relapse shortly afterward; symptoms apt to recur if treatment discontinued; general condition greatly improved; gained 20 lb.; vital capacity slightly reduced |
| 14 | 3 yr. | 18 yr. | 15 yr. | None | *Respiratory streptococcal infection* at 3; bronchopneumonia; pneumonia (?) at 7 yr. | Very poor; pneumonia right middle lobe; emphysema | 15 mo. | Greatly improved, gained 14 lb., symptoms apt to recur if treatment discontinued; vital capacity moderately reduced |
| 15 | 3 yr. | 15 yr. | 12 yr. | Mother; chronic bronchitis | *Pertussis* at 3; many acute exacerbations | Seriously ill; extreme respiratory difficulties; pulmonary fibrosis | 15 mo. | Moderately improved; several severe relapses if treatment discontinued; vital capacity moderately reduced |

condition cleared up slowly under penicillin given parenterally and by aerosol, combined with postural drainage, aminophyllin, and the like. At the time of the last examination, Feb. 2, 1948, the child was in good health, the only remaining symptom being slight wheezy dyspnea on exertion.

As became evident from the cases here tabulated and from many more cases not included in this series, the early results of penicillin aerosol treatment were very favorable in almost all patients with bronchopulmonary infection. In patients with early infection, the respiratory symptoms usually subsided within a week. Clinical findings indicative of tracheobronchitis disappeared after one to two weeks' treatment; resolution of a subacute bronchopneumonic process took place in one to two months. With continued treatment, the accomplished improvement of both the respiratory infection and the general condition became more and more obvious. Continuous normal temperature, increasing appetite, and a feeling of well-being proved the beneficial systemic reactions resulting from this therapy. Exposure to inclement weather and to physical exercise no longer was followed by an aggravation of the condition. Banal respiratory infections such as coryza no longer "settled down" in the chest. If an associated bacterial infection of the upper respiratory system was present, it usually cleared up, too. Coexisting true allergic manifestations were not influenced by the antibiotic. However, it became obvious that hypersensitivity to known allergens rarely caused a severe, uncontrollable condition as long as the infection remained subdued. In children whose asthma appeared to be related to bronchial infection alone, the asthma disappeared together with the other respiratory symptoms whenever the bronchial infection could be eliminated.

In patients with more advanced infection, especially if pulmonary fibrosis and emphysema had developed, the therapeutic effect was less prompt and complete. Nevertheless, the accomplished improvement surpassed by far, even in these instances, the results of previous treatments. As long as penicillin aerosol therapy was continued, and in a number of cases for a prolonged period after its termination, the respiratory symptoms were at least greatly reduced and the general condition improved to a great extent. Gains in weight of 10 pounds within the first few weeks were not unusual. The school attendance of many of the children, who before had missed several weeks every year, became more regular again and frequently as normal as that of other children; exercises such as skating were much better tolerated.

However, the follow-up of the fifteen children clearly demonstrated that favorable early results do not always indicate the actual arrest of the infection, especially in children who had been severely ill for many years. It is difficult to say whether in a given patient the recurrence of bronchopulmonary infection was due to a new infection or whether a residual infection had become active again. It appears that the tendency to relapses was less pronounced in patients with early infection than in those whose illness was of long duration with preceding exacerbations and intervening respiratory infections. Moreover, the recurrence of respiratory symptoms whenever they appeared could, in mild cases, be easily controlled by a short consecutive course with penicillin aerosol,

whereas in patients with definitely chronic conditions, relapses frequently occurred as soon as penicillin aerosol was discontinued, and a more intensive treatment was then required. In these patients the response to the antibiotic was similar to that in patients with frank bronchiectasis, even if no bronchial dilatation could be demonstrated by lipiodol studies. As in bronchiectasis, the sputum never became free from pyogenic organisms, or the condition persisted to some extent, even in the absence of these bacteria.

## SUMMARY

The prospects for prevention of chronic bronchitis and bronchiectasis largely depend on recognition and eradication of the initial bronchopulmonary infections at the earliest possible stage. Thus far, penicillin aerosol treatment seems the best available method for achieving the latter. It may be that more potent methods will be developed in the future. However, the most effective treatment cannot secure permanent cure, even in the mildest cases, if patients do not obtain the same attention after their recovery as given to patients with other fundamentally chronic diseases. The follow-up method used in rheumatic fever, tuberculosis, and the like should be applied also to children with potential bronchiectasis, in order to give undelayed treatment in the case of a relapse before it adds new damage to the respiratory system.

The prognosis for arrest of definitely chronic cases by penicillin aerosol therapy alone is less favorable. Nevertheless, encouraging results have been obtained by this new method, even in children with pulmonary fibrosis and emphysema. Therefore, the hope seems to be justified that penicillin aerosol treatment, combined with other methods such as bronchoscopic aspiration of bronchial secretion and systematic postural drainage, may eventually lead to the arrest of the condition. Such therapeutic measures against the local disease must be supplemented by measures directed toward improvement of the general health. As in tuberculosis, a prolonged convalescence in healthful surroundings appears essential in all but the mildest cases.

Most of all, it should be realized that this common and apparently communicable infection is a public health problem. It is true that the condition has less spectacular features than certain other diseases which, although less common, attract wider attention. However, its often serious character and the great economic burden upon the individual and the community should be sufficient reasons for recognizing that here, too, possible prevention is a sounder approach than belated curative efforts. Since the disease is prevalent in poor families, chest clinics and public convalescence homes for nontuberculous pulmonary disease are needed. Finally, public enlightenment about prophylactic measures and greater knowledge among the coming generation of physicians will give a strong impulse to individual efforts in the prevention of chronic bronchitis and bronchiectasis.

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# EARLY WHOOPING COUGH IMMUNIZATION

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THIS paper relates our experiences with whooping cough immunization in infants under 6 months of age, using alum-precipitated vaccine. The purpose of the investigation is threefold: first, to determine if Sako's[1] work on early whooping cough immunization could be repeated; second, to correlate the Flosdorf[2] skin test with the rapid slide agglutination test; third, to observe the incidence of local and systemic reactions.

## MATERIALS AND METHODS

Since 1946 the city of Dallas has been furnished whooping cough vaccine by the Texas State Laboratory. The vaccine is phase I of *Hemophilus pertussis*, alum-precipitated, and standardized to contain 40 billion organisms per cubic centimeter. The infants in this study were white, Negro, and Mexican who attended the City Well-Child Conferences. They were immunized with 0.2 c.c., 0.3 c.c., and 0.5 c.c. of this vaccine at four-week intervals for a total of 1.0 c.c. Some infants in this series received their first injection at 2 weeks of age. The greatest number began their immunization at one month of age, which was usually the time of their first visit.

The agglutination test* was performed by the rapid slide method of Powell and Jamieson.[3] The procedure followed was exactly as described by them. Care was taken not to rock the card more than one minute. In forty infants the antigen used was first centrifuged, the supernatant fluid poured off, and the antigen resuspended in albumin. No difference was noted in the results with the albumin-suspended antigen when compared with the usual antigen.

The skin test† of Flosdorf was performed by injecting 0.1 c.c. of the agglutinogen intracutaneously into the forearm. The area of induration was measured at the end of twenty-four hours. An area of 10 mm. or more was considered an immune or positive reaction. All tests were performed by us.

The first 117 infants receiving skin and agglutination tests prior to the first injection of whooping cough vaccine served as controls. All infants had the skin and agglutination tests performed three to four months after the last whooping cough injection. A form was devised which had the child's name, address, age, sex, date of injection, type of reactions, and results of tests. The reactions looked for were fever, induration, and abscess. The mothers were questioned about fever. This was quite unreliable since very few mothers used a thermometer. The presence of induration and abscess was noted by us. The

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*The material for this test was furnished by Eli Lilly & Company, Indianapolis.

†In this test the agglutinogen was supplied by Sharp & Dohme, Inc., Philadelphia.

vaccine was given by the City Health Nurses, who were instructed as follows: (1) Use a clean dry needle; (2) inject deeply and distally into the deltoid; (3) use a small amount of air to clear the needle.

## RESULTS

Table I reports the results of the skin and agglutination tests in 117 infants before their first injection of whooping cough vaccine. None of the infants in the group showed a positive skin test. Sixteen had positive agglutination tests. Mothers of the infants with positive agglutination tests were also tested and showed similar results. However, a number of mothers with positive agglutination tests had infants who showed negative agglutination tests.

The infants were divided into two groups, A and B. In Group A, immunization was completed before the end of the fourth month. In Group B, it was completed between the fourth and sixth months. (See Tables II and III.)

In Group A there were twenty-two infants who received their first injection at 2 weeks, and their immunization was completed at 10 weeks. All of these responded well as judged by these tests. The infants with negative skin reactions had positive serum agglutinations, and those with negative agglutination tests had positive or immune skin reactions. Thus no infant in the entire series had both a negative skin reaction and a negative serum agglutination.

Table I. Infants Tested Before Whooping Cough Vaccine Was Administered

| AGGLUTINATION TEST | | | SKIN TEST | |
|---|---|---|---|---|
| NEGATIVE | WEAKLY POSITIVE | STRONGLY POSITIVE | NEGATIVE | POSITIVE |
| 101 | 13 | 3 | 115 | 2 (doubtful) |

Table II. Infants in Whom Immunization Was Completed Before the Age of 4 Months (Group A)

| AGGLUTINATION TEST | | | SKIN TEST | |
|---|---|---|---|---|
| NEGATIVE | WEAKLY POSITIVE | STRONGLY POSITIVE | NEGATIVE | POSITIVE |
| 10 | 37 | 68 | 3 | 112 |

Table III. Infants in Whom Immunization Was Completed Between the Ages of 4 and 6 Months (Group B)

| AGGLUTINATION TEST | | | SKIN TEST | |
|---|---|---|---|---|
| NEGATIVE | WEAKLY POSITIVE | STRONGLY POSITIVE | NEGATIVE | POSITIVE |
| 1 | 14 | 45 | 4 | 56 |

Table IV. Incidence of Reactions in Group A

| NUMBER OBSERVED | NO REACTION | FEVER | INDURATION | FEVER AND INDURATION | ABSCESS |
|---|---|---|---|---|---|
| 106 | 75 | 4 | 11 | 13 | 3 |

Table V. Incidence of Reactions in Group B

| NUMBER OBSERVED | NO REACTION | FEVER | INDURATION | FEVER AND INDURATION | ABSCESS |
|---|---|---|---|---|---|
| 35 | 35 | 3 | 8 | 9 | 0 |

It should be noted that the induration usually was small and that often the mother was completely unaware of it. Fever was rarely high or of long duration. In the three children with abscess formation the process cleared spontaneously and apparently did not affect the infants. During the two years of this study none of the infants in this series was reported to us as having developed whooping cough.

## DISCUSSION

Sako and his associates,[4] and later Sako[1] alone, immunized a very large series of infants under 3 months of age with alum-precipitated whooping cough vaccine. They demonstrated conclusively that this was an effective immunologic procedure as judged by clinical and serologic results. Waddell and L'Engle,[5] using a fluid vaccine with a total dose of 100 billion organisms, inoculated 129 infants beginning at the age of one week, and observed that many responded with a very satisfactory titer. Recently Adams, Kimball, and Adams[6] noted in a small series of infants under 3 months of age that fluid vaccine produced a rise in antibody titer in many of them.

In the series of Sako and his associates,[4] the incidence of whooping cough was greater in the group of infants immunized before the age of 6 months than in the older group. However, there were no deaths, and the disease was milder in the immunized group when compared with unvaccinated infants. On the basis of these studies, Sako and later Waddell and L'Engle recommend that whooping cough vaccine injections be instituted at one month of age.

Lapin[7] stated that whooping cough vaccine was without value in young infants. He said that "Theoretical analogy with other immunizations and Sauer's discouraging results under 6 months more than counterbalance the recent report of Sako and his associates." It should be pointed out that while in 1941 Sauer[8] reported he could not protect young infants as successfully as he did those over 7 months, he had no deaths and the disease was milder in the immunized group. Sauer[9] now believes that with the use of alum-precipitated vaccine he can obtain results in young infants that are quite comparable to those over 7 months.

This investigation was planned to conform with the studies of Sako and his associates.[4] We repeated his work, using the same type of vaccine with an identical dosage scheduled and the same age group of infants. Our results in this much smaller group as judged by serologic and skin tests are very similar to Sako's. The incidence of reactions is about the same. Fever is scarcely ever observed; however, in private practice fluid vaccine leads to many more febrile reactions. Induration is only slight and often overlooked by the mother. Abscess formation is not distressing; however, it is a cause of anxiety in the mothers. It appeared in one white infant and two Negro infants in our series and in each case the abscess healed spontaneously. We believe it can largely be avoided by the use of a dry needle, injecting deeply and distally into the upper arm, and following with 0.1 c.c. of air to clear the needle.

It seems that the procedure of using alum-precipitated vaccine, standardized to contain 40 billion organisms per cubic centimeter and given in doses of 0.2 c.c.,

0.3 c.c., and 0.5 c.c. at monthly intervals to infants at one month of age is very effective. Moreover, it appears to be the most valuable method available at present for reducing the mortality and morbidity rate in infants under 6 months of age.

It is not the purpose of this paper to enter into a lengthy discussion of the value and reliability of the agglutination and skin tests. Suffice it to say that the establishment of the clinical effectiveness of a pertussis vaccine, as has been pointed out by numerous students of this problem, is extremely difficult. Comparable groups of vaccinated and nonvaccinated children are almost impossible to obtain. Moreover, the severity of the disease varies from year to year and with different localities. In addition, it is quite conceivable that *Bacillus parapertussis* may account for some cases of so-called whooping cough.

For these reasons most investigators have resorted to various laboratory tests to determine the effectiveness of pertussis vaccine. The mouse protection test,[10] the agglutination test,[3, 11] the complement fixation test,[9] the opsonocytophagic test,[12-14] and the skin test of Flosdorf[15, 16, 20] have all been used as a measure of the efficacy of pertussis vaccine. Lapin[17] has summarized the pros and cons of the various tests. When more than one test has been done, a fair degree of correlation has been noted.[19-22] It appears that these different tests measure various aspects of the same immunologic process.

In the present study the agglutination tests were made by the rapid slide method of Powell and Jamieson.[3] This test has been correlated with the quantitative test by Sako and his associates.[1, 4] They found that a moderately positive and a strongly positive rapid agglutination test indicated a titer of 1:160 or more. Sako, in a personal communication, stated that if the rapid slide agglutination method is done correctly and the individual develops experience with it, the test is a reliable one. DeGara and Mayer[23] correlated the slide agglutination test with the quantitative method. When one studies their results it is apparent that the slide method errs on the low side, that is to say it will be negative when the tube method is negative or shows a low titer. When the slide method is strongly positive the titer is always high. It is only with the weakly positive slide agglutination that one may miss some of the higher titers. Mishulow[26] observed a close relationship between the two methods.

Miller and his associates[18] and later Sako[1] demonstrated that clinical immunity corresponded to the agglutination titer. No children with a titer of 1:320 or more developed whooping cough. However, there were those with a negative agglutination test who did not take whooping cough after exposure. Felton and Flosdorf[24] felt that the children who were protected in the absence of circulating antibodies had cellular antibodies present as measured by a positive skin test.

The Flosdorf skin test appears to be a reliable method for detecting susceptibles and the effectiveness of whooping cough vaccine. Felton and Flosdorf[24] and Felton and his associates[25] have observed a close correlation between the agglutinogen skin test and the clinical and agglutination methods. Sauer and Markley[20] compared the skin test with the complement fixation reaction and observed a good correlation between them.

Reference to Table I shows that there were sixteen infants with demonstrable humoral antibodies before the first injection of whooping cough vaccine. The passage of maternal antibodies of whooping cough has been observed by others. The skin tests were negative in all but two infants, and in them it was doubtful. This is in agreement with Felton and Flosdorf,[24] who never found a positive skin test in young nonimmunized infants. Apparently the passage of antibodies in the infants has no effect upon cellular antibody formation.

Tables II and III demonstrate that there is a high degree of correlation between the rapid slide method and the skin test. We do not have a satisfactory explanation for the fact that a few infants had positive agglutination tests with negative skin reactions. This might be due to the fact that the area of induration, although less than 10 mm., signified immunity. Perhaps some of these children would have shown a delayed positive reaction if observed on the fifth day. Sauer and Markley[20] have observed infants with humoral antibodies as measured by the complement fixation test who had negative skin reactions.

We agree with Tucker[27] that the agglutinogen skin test is simple, reliable, and specific. Perhaps 10 mm. is too large an area of induration to differentiate the immune from the susceptibles. Were this true, it would explain the negative skin reaction in the infants with positive agglutination tests. It may be that any area of induration is significant. We are now investigating this point.

## SUMMARY

Whooping cough immunization with an alum-precipitated vaccine containing 40 billion organisms per cubic centimeter given in doses of 0.2 c.c., 0.3 c.c. and 0.5 c.c. at monthly intervals was used in infants of one month of age or less. It proved to be an effective immunologic procedure as judged by clinical, serologic, and skin tests. Reactions were minimal and abscesses uncommon. If the proper technique is used in administering the vaccine, abscess can perhaps be eliminated. The agglutinogen skin test and the rapid slide agglutination method showed a high degree of correlation. The skin test is a simple, reliable, and effective method for determining immunity following pertussis immunization.

The authors wish to thank Dr. J. W. Bass, Director of the Health Department, and the nurses of the Health Department for their very kind cooperation. Without their interest and aid this study could not have been made.

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# HEART DISEASE IN SAN FRANCISCO SCHOOL CHILDREN

## 1947 Registry Showing Incidence, Problems, and Supervision Techniques

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RECOGNITION of the need for a close check on rheumatic fever as on tuberculosis has led San Francisco to pioneer in the establishment of a central registry of cardiac children in its schools. The question of the incidence of heart disease, particularly of rheumatic fever and rheumatic heart disease, has been an unanswered one in this area for many years. The central registry was devised, therefore, to serve a double purpose: case finding, and follow-up. This registry was started at the beginning of the school term in September, 1946. By the end of the June, 1947 term there were 1,120 children with heart disease known to the registry. In this registry we have attempted to include as much vital information as possible regarding each child. Our sources of information were many:

1. School nurses submitted lists of all children in their schools known to have cardiac disease. These lists were compiled from reports of school physicians and private physicians and clinics caring for the children.
2. Physicians reported new cases of rheumatic fever. This is required by law in California.
3. Many children had their cardiac status clarified by examinations in 100 of the 153 schools served by the San Francisco Department of Public Health, a study to be subsequently described.
4. The files of the School Diagnostic Center of the San Francisco Department of Public Health revealed many of the cases.
5. A major source of information regarding active cases of rheumatic fever proved to be the requests for home teachers for the children.
6. Reports to the Crippled Children's Services of the San Francisco Department of Public Health supplemented other sources.

There have been previous surveys of this problem in San Francisco. One by Ina Richter[8] in 1931 included children examined at the School Diagnostic Center of the San Francisco Department of Public Health during the years 1929 to 1931. A second study in 1937 by Sampson and his associates[10] included not only the cases examined at the School Diagnostic Center but a survey of 295 children examined in the schools by Dr. John Sampson. We shall indicate the similarity between our studies and those of the previous workers, particularly the one completed ten years ago.

It is to be emphasized that this registry is a current one—i.e., it includes only those children about whose cardiac status definite information was received

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TABLE I. RHEUMATIC CHILDREN KNOWN TO CENTRAL CARDIAC REGISTRY SEPTEMBER, 1946, TO JUNE, 1947

| DIAGNOSIS | BOYS 5-10 YRS. | BOYS 10-18 YRS. | GIRLS 5-10 YRS. | GIRLS 10-18 YRS. | PRE-SCHOOL | TOTAL |
|---|---|---|---|---|---|---|
| Active rheumatic fever | 33 | 46 | 30 | 77 | 11 | 197 |
| Known recurrent rheumatic fever | | 3 | 8 | 17 | | 28 |
| Questionable rheumatic fever | 4 | 3 | 7 | 6 | | 20 |
| Rheumatic heart disease | 18 | 86 | 13 | 82 (1 SBE) | | 199 |
| Potential rheumatic heart disease | 42 | 91 | 25 | 75 | 1 | 234 |
| Rheumatic and congenital | | 6 | 1 | 1 (active) | | 8 |
| Rheumatic vs. congenital | 4 | 4 | 2 | 5 | | 15 |
| Rheumatic vs. functional | 5 | 19 | 2 | 21 | | 47 |
| Totals | 106 | 258 | 88 | 284 | 12 | 748 |

TABLE II. CHILDREN WITH CONGENITAL HEART DISEASE IN CENTRAL CARDIAC REGISTRY, SEPTEMBER, 1946, TO JUNE, 1947

| DIAGNOSIS | BOYS 5-10 YRS. | BOYS 10-18 YRS. | GIRLS 5-10 YRS. | GIRLS 10-18 YRS. | PRE-SCHOOL | TOTAL |
|---|---|---|---|---|---|---|
| I.V. septal defect | 16 | 24 | 16 | 25 | | 81 |
| I.A. septal defect | 11 | 2 | 6 | | | 19 |
| Patent ductus | 2 | 4 | 6 | 6 | 1 | 19 |
| Other types | 20 | 22 | 16 | 14 | 2 | 74 |
| Congenital vs. functional | 6 | 16 | 6 | 14 | 5 | 47 |
| Totals | 55 | 68 | 50 | 59 | 8 | 240 |
| *Other Diagnoses* | | | | | | |
| Organic vs. functional | 22 | 33 | 16 | 16 | 2 | 89 |
| Being followed to complete diagnosis | 3 | 14 | 6 | 13 | | 36 |
| Miscellaneous | | 4 | | 3 | | 7 |
| Totals | 25 | 51 | 22 | 32 | 2 | 132 |
| Grand Total Cardiac Children in Registry to Date (Tables I and II) | | | | | | 1,120 |

during the school year of September, 1946, to June, 1947. A summary of this registry is shown in Tables I and II.

*Table I: Rheumatic Children Known to Central Cardiac Registry, September, 1946 to June, 1947.*—It can be seen that there were 225 children with active rheumatic fever, of which only twenty-eight were known to have recurrent cases. If we include those in whom the diagnosis was in doubt, there was a total of 245 children with active rheumatic fever during the nine months represented. (Eleven of these children were of preschool age.) This does not include children admitted to San Francisco hospitals from other parts of the state.

In addition there were 199 children with inactive rheumatic heart disease but with classical signs of rheumatic valvulitis. It is to be emphasized that we were very conservative in our diagnoses. Those with signs which were at all questionable were placed in other categories.

There were 234 children with potential rheumatic heart disease, further defined by us as children known to have had rheumatic fever within the past ten years but at this time showing no characteristic evidence of heart disease. There were eight cases which we believe represented rheumatic heart disease superimposed upon a known congenital lesion, usually an interauricular septal defect.

The remainder were those doubtful patients previously mentioned in whom we could not make a more accurate diagnosis at that time.

*Table II: Children With Congenital Heart Disease in Central Cardiac Registry, September, 1946 to June, 1947.*—There were 240 children with congenital cardiac defects. This group was almost as large as the group with active rheumatic fever. The most common lesion was the patent interventricular septal defect, of which there were eighty-one. There were nineteen children with interauricular septal defects, and the same number with a patent ductus arteriosus. The remainder, including children with the cyanotic types and such diagnoses as subaortic stenosis and coaretation of the aorta, are grouped together under one heading but are rapidly being classified as information is obtained. There were forty-seven children in whom the findings were such that a definite differentiation between a congenital lesion and a nonorganic functional murmur was not made at the time. All of the latter will be followed at regular intervals.

Thus the total number of children known to have either actual or potential heart disease totals 1,120. We are convinced, however, that this represents an absolute minimum in all categories.

We feel that the great value of the registry is that it shows more than mere figures. It includes the essential personal history of each child, including the type of medical supervision, hospital admissions, convalescent care, follow-up reports, and any other information which will aid in determining the current cardiac status of each child, and ultimately, to the better integration of his total care. In this respect we have followed the London County Council's Rheumatic Scheme, first organized in 1926.

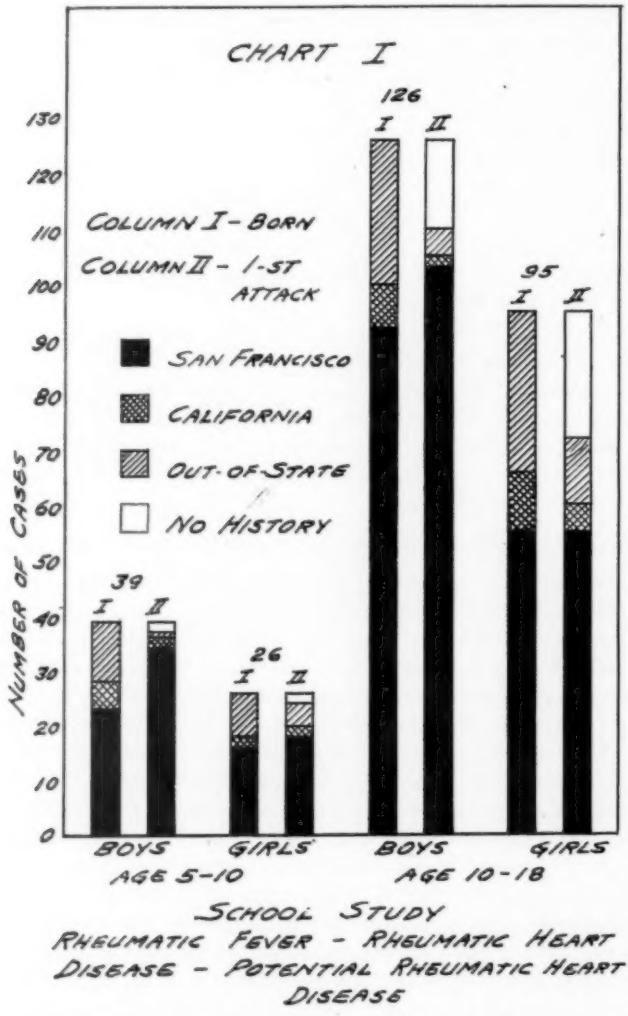
## SCHOOL STUDY: SURVEY OF HEART DISEASE IN 100 SAN FRANCISCO SCHOOLS

The following is the report of a survey of cardiac disease made in 100 San Francisco schools, including elementary, junior high, and high schools, both public and parochial. The population of the schools which we visited was approximately 57,768, more than half of all children attending San Francisco schools. We examined only those children who had previously been selected by either school physician, private physician, or clinic, and some suspects chosen by the school nurse from history and observation. In other words, we examined only those children already suspected to have cardiac disease.

Altogether in the school check we examined 698 children between the ages of 5 and 18 years. These children were examined in their own schools or in nearby health centers during the school year of September, 1946, to June, 1947. During the first term one of us (S. J. R.) made all of the examinations; during the second semester another worker joined the project (D. M. A.). The chief purpose in performing these examinations was to determine the current status of children listed by the school nurses as having a history of cardiac disease or rheumatic fever as reported to them in turn by a private physician, clinic, or the school physician. Thus we planned to examine only known cardiac suspects. That we found nine children with active rheumatic fever attending school was an accidental, if important, product of our work. We were also interested in

determining the medical supervision of these children. Although all of them were presumed to have cardiac disease, 17.4 per cent of them were found to have no medical supervision of any kind.

*Table III: School Survey.*—It can be seen that of the 199 children known to the cardiac registry as having rheumatic heart disease, 111 were examined in




school by the authors. The nine children with active rheumatic fever were found accidentally. While we were at the school an astute nurse would ask us to examine a child with suspicious symptoms, chiefly fatigue or pallor. These

children were immediately referred to proper medical supervision and were subsequently hospitalized, put to bed at home, or sent to convalescent institutions. Each of them was proved to have acute or subacute rheumatic fever.

The children with congenital lesions plus rheumatic heart disease have been previously mentioned. There were nine of these. There were 171 children with a history of rheumatic fever in whom we could find no definite evidence of cardiac involvement at this time. These children we classified as having potential rheumatic heart disease.

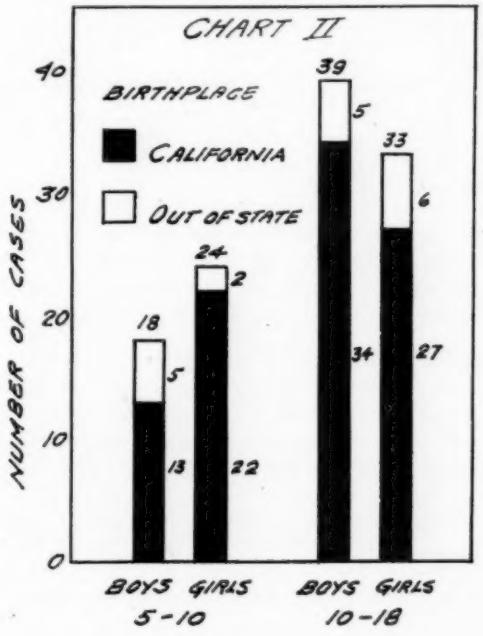



*Table IV: School Study.*—There were 114 children with congenital lesions, of whom thirteen would be considered operable at the present time. Some of these have since undergone operation. The remaining children represent miscellaneous or doubtful cases. As in other surveys, we found 195 children in whom there was no evidence or history of cardiac disease although they had been considered cardiac suspects. They included children with murmurs which we did not consider to represent cardiac disease—i.e., functional heart murmurs.

*Tables V and VI* show the comparison of our findings with those of Sampson and his associates in 1937. Although his examinations represented a smaller number of the school population, it can be seen that there is no marked difference

TABLE III. SUMMARY OF RESULTS OF EXAMINATIONS IN 100 SAN FRANCISCO SCHOOLS*

| RHEUMATIC HEART DISEASE | NO. OF CHILDREN |
|---|---|
| Children with rheumatic heart disease | 111 |
| Children with active rheumatic fever attending school | 9 |
| Children with rheumatic plus congenital heart disease | 9 |
| (Children who have signs of congenital heart disease and in addition, have a history and signs which are indicative of superimposed rheumatic heart disease.) | |
| Children with potential rheumatic heart disease | 171 |
| (Children with a definite history of rheumatic fever within the last ten years but who have no evidence of cardiac involvement at this time.) | |
| Rheumatic vs. congenital | 12 |
| (Children with organic heart disease not differentiated by means at our disposal at time of examination.) | |
| Rheumatic vs. functional | 23 |
| (Children with no history of rheumatic fever but with signs which were suspicious of cardiac involvement.) | |
| Total | 335 |

| | |
|---|---|
| *School population represented | 57,768 |
| Total children examined | 698 |
| Per cent of population examined | 1.2 |

TABLE IV. SUMMARY OF RESULTS OF EXAMINATIONS IN 100 SAN FRANCISCO SCHOOLS

| CONGENITAL HEART DISEASE | | NO. OF CHILDREN |
|---|---|---|
| Interauricular septal defects | | 26 |
| Interventricular septal defects | | 61 |
| Other defects | | 27 |
| Patent ductus arteriosus | 9 | |
| Tetralogy of Fallot | 3 | |
| Coaretation of aorta | 1 | |
| Unspecified | 14 | |
| Congenital vs. functional | | 19 |
| (Children in whom at the time of examination no differentiation could be made between nonorganic signs and those indicative of a congenital heart lesion.) | | |
| Organic vs. functional | | 26 |
| (Children with no history but with signs which could not be differentiated, i.e., as between functional heart murmur, rheumatic or congenital heart disease.) | | |
| Miscellaneous | | 6 |
| (2 hypertension, 1 thyrotoxic heart disease, 1 sickle cell anemia, 1 erythroblastic anemia, 1 gonorrheal (arthritis.) | | |
| Undetermined | | 3 |
| Children with no evidence nor history of cardiac disease although labeled as cardiac suspects (functional murmur) | | 195 |
| Total | | 363 |

TABLE V. INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 197 CARDIAC SUSPECTS FOUND AMONG 13,338 SCHOOL CHILDREN IN 1937*

| SCHOOL POPULATION REPRESENTED | HEART DISEASE SUSPECTS | ORGANIC HEART DISEASE | RHEUMATIC | | CONGENITAL | | RATES PER 1,000 SCHOOL POPULATION | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | TOTAL | % | TOTAL | % | ORGANIC | RHEUMATIC | CONGENITAL |
| 1,338 | 197 | 49 | 30 | 62 | 19 | 38 | 3.7 | 2.2 | 1.4 |

*Sampson, Christie, and Geiger[10]

in the final results. Sampson found that 62 per cent of his cases of total organic heart disease represented rheumatic involvement, while we found the figure to be 55.3 per cent. We found a higher percentage of congenital lesions, 44.7 per

cent as compared with 38 per cent by Sampson. As will be seen in Table VII, this percentage difference between rheumatic and congenital heart disease is almost identical with that found by Rauh[7] in Cincinnati schools in 1938. We would like to emphasize that the rheumatic children we examined were of necessity in the inactive phase. The incidence of 4.4 per 1,000 does not include the 245 children with active rheumatic fever, many of whom will undoubtedly develop a valvulitis.

TABLE VI. INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 698 CARDIAC SUSPECTS FOUND AMONG 57,768 SCHOOL CHILDREN IN 1947*

| SCHOOL POPULATION REPRESENTED | HEART DISEASE SUSPECTS | ORGANIC HEART DISEASE | RHEUMATIC | | CONGENITAL | | RATES PER 1,000 SCHOOL POPULATION | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | TOTAL | % | TOTAL | % | ORGANIC | RHEUMATIC | CONGENITAL |
| 57,768 | 698 | 255 | 141 | 55.3 | 114 | 44.7 | 4.4 | 2.43 | 1.9 |

*Robinson, Aggeler, and Daniloff, September, 1946 to June, 1947.

In summary, we found that 4.4 children per 1,000 school population had organic heart disease, of which 2.43 per 1,000 had rheumatic heart disease (inactive) and 1.9 per 1,000 had congenital heart disease. To interpose Dr. Ina Richter's[8] figures of 1929-1931, she examined 319 children with organic heart disease at the School Diagnostic Center, of whom 151, or 47 per cent, had rheumatic heart disease, and 140, or 44 per cent, had congenital heart disease.

*Table VII* shows the incidence of heart disease in school children in other cities. A direct comparison is not accurate because of the various age groups and types of examinations performed. However, it can be seen that those studies which assumed that 80 per cent of organic heart disease was rheumatic in origin may well be subject to some revision. In a late study in Washington County, Iowa, which involved a small number of school children, Jackson[4] found that 58 per cent had rheumatic heart disease and 42 per cent had congenital heart disease.

### RHEUMATIC FEVER INDIGENOUS TO CALIFORNIA

In the school study we also tried to ascertain where the children acquired the rheumatic fever. There has been a consistent tendency to state that most cases of rheumatic fever and rheumatic heart disease in California were the result of the migration from the East and Middle West. Dr. Helen Johnson,[14] in a study covering five years in Contra Costa and Solano Counties, California, found that 81.4 per cent of all children with rheumatic heart disease, when the history of rheumatic fever could be obtained, had their first attack in California.

Chart I shows that 286 children in the school study had either a history of rheumatic fever or evidence of rheumatic heart disease. The number born out of state was seventy-four, but of these, only twenty-two had their known initial attack of rheumatic fever out of the state, which gives an incidence of 80 per cent who had their first attack of rheumatic fever in California. Davis and Rosin[3] studied the hospital admissions to Los Angeles County Hospital for rheumatic fever between the years 1936 and 1941. There were 157 patients with

TABLE VII. INCIDENCE OF HEART DISEASE IN SCHOOL POPULATIONS OF CITIES IN THE UNITED STATES

| CITY | NUMBER OF SCHOOL CHILDREN REPRESENTED | NUMBER EXAMINED IN SURVEY | AGE | SEX | ORGANIC HEART DISEASE PER 1,000 | RHEUMATIC HEART DISEASE PER 1,000 | CONGENITAL HEART DISEASE PER 1,000 |
|---|---|---|---|---|---|---|---|
| San Francisco (Author Survey, 1946-1947) | 57,678 | 698 | 5-18 | M. & F. | 4.4 | 2.43 | 1.9 |
| San Francisco[10] (1937) | 13,338 | 197 | 5-19 | M. & F. | 3.7 | 2.2 | 1.4 |
| Denver[12] (1945) | 1,051 | 114 | 12-19 | M. & F. | | 4.8 | |
| Eureka, Calif.[11] (1939-1941) | 2,450 | 2,450 | 5-19 | M. & F. | 20.7 | 20.0 | 0.7 |
| Denver[12] (1945) | 1,845 | 1,845 | 12-19 | F | 19.0 | 16.3 | 2.7 |
| Redlands, Calif.[11] (1939-1941) | 2,635 | 2,635 | 5-19 | M. & F. | 4.6 | 3.8 | 0.8 |
| Susanville, Calif.[11] (1939-1941) | 732 | 732 | 5-19 | M. & F. | 1.5 | 1.1 | 0.4 |
| Cincinnati[1] (1927) | 6,960 | | | | 3.7 | | |
| Cincinnati[7] (1938) | 85,389 | 1,782 | 5-19 | M. & F. | 3.6 | 2.0 | 1.6 |
| Philadelphia[2] (1937) | 33,293 | 863 | 6-18 | M. & F. | 5.9 | 5.0 | 0.9 |
| Louisville, Ky.[13] (1941) | 41,905 | | 6-15 | M. & F. | 5.2 | 3.6 | 1.6 |
| Boston[9] (1927) | 119,337 | 2,311 | 6-15 | M. & F. | 5.0 | 4.5 | 0.5 |
| Washington Co., Iowa[4] (1945) | 5,058 | 5,058 | 5-19 | M. & F. | 4.7 | 2.72 | 1.98 |

this diagnosis admitted to the Pediatric Department during this period. Of these, 103, or 65.7 per cent, were born and reared in Los Angeles. Of the fifty-four children born out of the city, forty-two had lived in Los Angeles for at least one year prior to the first attack. While we did not explore the familial incidence of rheumatic fever in those children born out of the state, we were impressed by the fact that those children born out of San Francisco came here to have their rheumatic fever.

Chart II shows the place of birth of children with congenital heart disease, which was also of interest to us. Of 114 children with congenital heart disease, ninety-six, or 85.1 per cent, were born in California, while only seventeen, or 14.9 per cent, were born out of the state. This finding refutes an oft-repeated statement that families with children who have congenital cardiac defects seek the milder climate of California.

While we divided the children by age groups, 5 to 10, and 10 to 18, and by sex also, we did not consider the results of sufficient significance to do more than note them, as can be seen in the tables and charts.

In conclusion, it may be stated that as of June, 1947:

1. There were over 1,000 cases of heart disease in children of school age in San Francisco known to an operating cardiac registry.

2. There were 234 cases of active rheumatic fever among the children 5 to 18 years of age and eleven cases in children of preschool age, a total of 245.

3. Out of every 1,000 school children, 2.43 had rheumatic heart disease—i.e., valvulitis. (This does not include 245 active cases.)

4. Almost 2 (1.9) out of every 1,000 had some type of congenital heart disease.

5. Eight-five per cent of the children with cardiac disease were born in San Francisco or somewhere in California, and were reared here.

6. The problem of preventable heart disease is a significant one in San Francisco, and measures for its prevention and control remain a major medical problem.

## PURPOSE OF REGISTRY

Since June, 1947, when 1,120 children were known to the central cardiac registry, a considerable number of children have been added. The figure changes every day. Many of the children counted in the June, 1947, figure as having potential rheumatic heart disease have had recurrences of rheumatic fever. New cases have been found. We want to stress the fact that this registry is not just a pack of cards. It provides a method of following these children through the years to be sure that they stay under medical supervision, that they may have hospital and other institutional care when indicated, that the circumstances of their lives may be eased when necessary, that they may have the proper education for their physical limitations, and that they may be protected in every way possible from the recurrent infections that are so dangerous to them.

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# FURTHER EXPERIENCE WITH THE HYPOXIA TOLERANCE TEST OF THE HEART IN CHILDREN

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THE preliminary report on the hypoxia tolerance test of the heart in children was published in 1946.[14] The normal cases as well as those with pathologic findings were few, but the results were so encouraging that further studies were made. Today our experience is greater; we have at this time examined 365 patients and taken about 600 tests. Since we have not been able to examine all cardiac patients in our clinic we have chosen special groups in accordance with our research plans during the last years.

The test is performed with a special apparatus previously described.[14] As a rule the children were given 9 per cent oxygen for a period of ten minutes. The effect of the test was measured by means of electrocardiography and phonocardiography, and in a few cases the arterial oxygen saturation was followed by means of an oximeter.

The age distribution of the cases is illustrated in Fig. 1.

Fig. 2 gives data regarding the cases in the normal group and those in the group with subjective symptoms but no clinical signs. As the latter group, in our opinion, does not contain any cases of real cardiac disease, both groups together could be looked upon as our normal material. In only two cases out of ninety-three have there been positive reactions.

Fig. 2 also shows forty-two cases of rheumatic heart disease, sixty-four cases of active and healed myocarditis, and forty-four cases of gallop rhythm, and represents the result of the tests made in acquired heart disease. In active rheumatic carditis about three-quarters of the cases have been positive. About 75 per cent of the patients with healed lesions (with or without a rheumatic valve disease) have reacted negatively. It is perhaps astonishing that there is such a high percentage of negative cases in this group, but it contains remarkably few cases of a more severe nature. On the whole it would seem that rheumatic heart disease in Sweden today is much rarer and milder than it was in previous years. The myocarditis group is not quite uniform. We have tried in this group to collect cases with clinical electrocardiographic or roentgenologic findings. The result has been about the same as for the rheumatic group. Thus, about 75 per cent of cases of active myocarditis (rheumatic cases of course excluded) have shown a positive result. The corresponding figure for patients with healed lesions is only 20.5 per cent. Out of forty-four patients with gallop rhythm without other signs of cardiac disease, more than one quarter (27.3 per cent) have given a positive reaction to the hypoxia test. This result, together with the result in the healed myocarditis group, speaks in favor of the opinion, empha-

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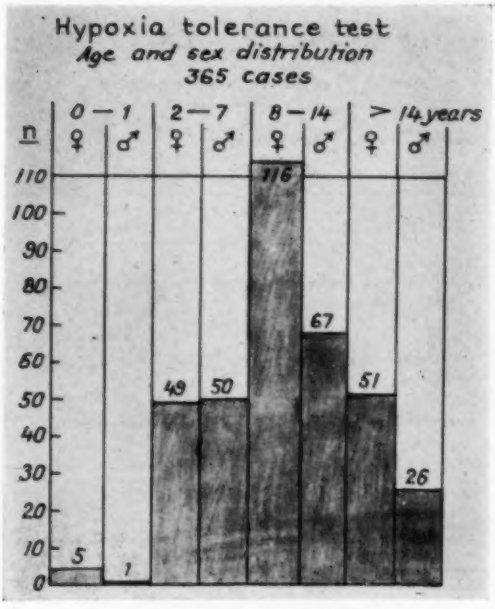


Fig. 1.—Age and sex distribution.

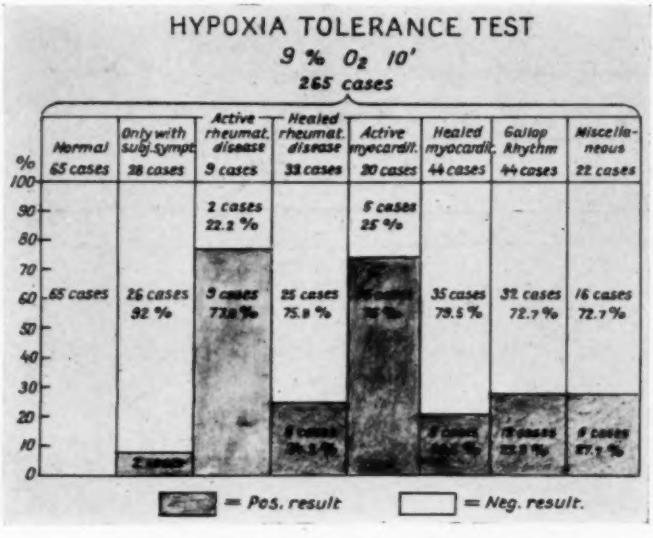


Fig. 2.—Normal cases and cases of acquired heart disease.

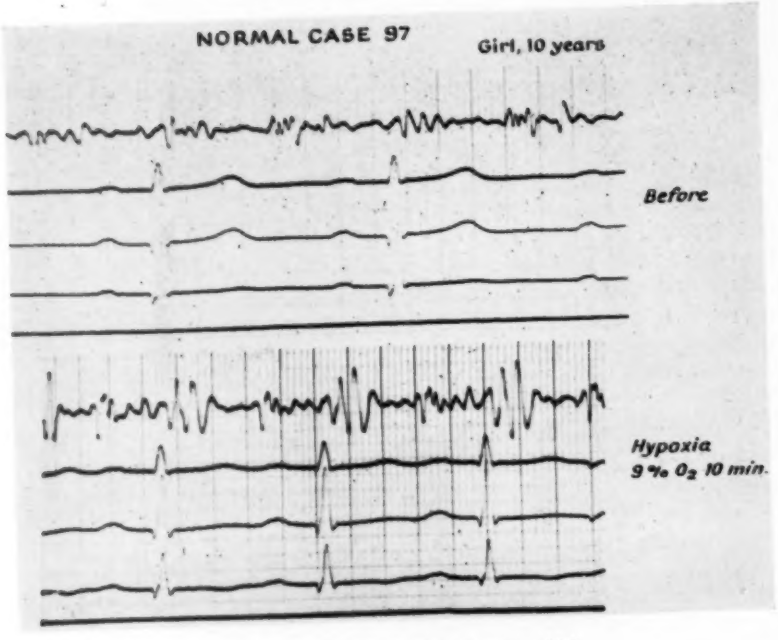


Fig. 3.—Normal case, girl, 10 years old.*

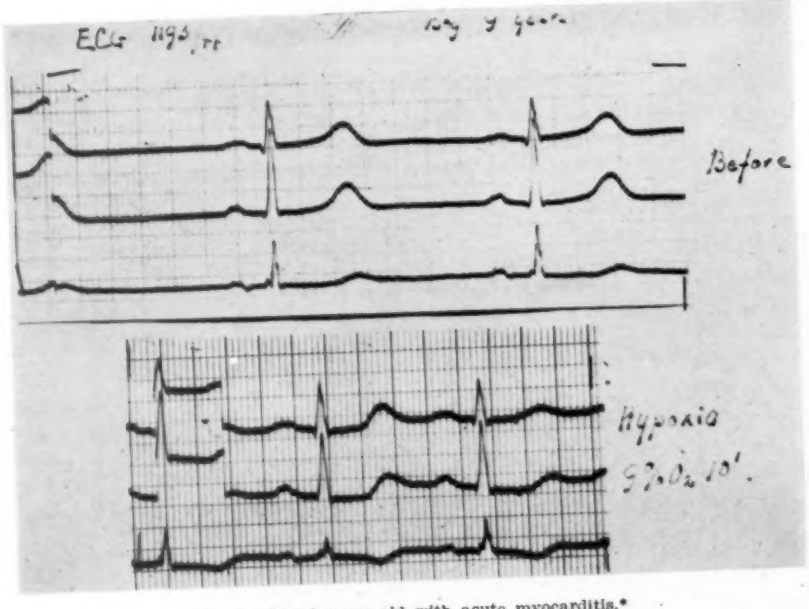


Fig. 4.—Boy 9 years old with acute myocarditis.*

*The time lines on the ECG charts are: thin lines, 1/10 second, or 0.02; thick lines, 1/10 second, or 0.1.

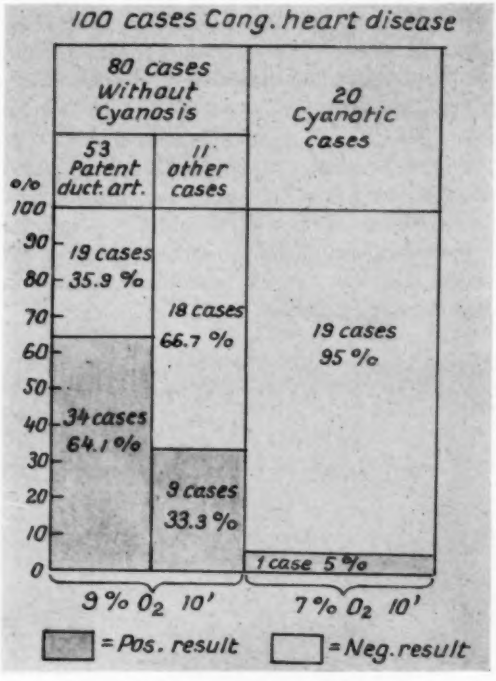


Fig. 5.—Congenital heart defects.

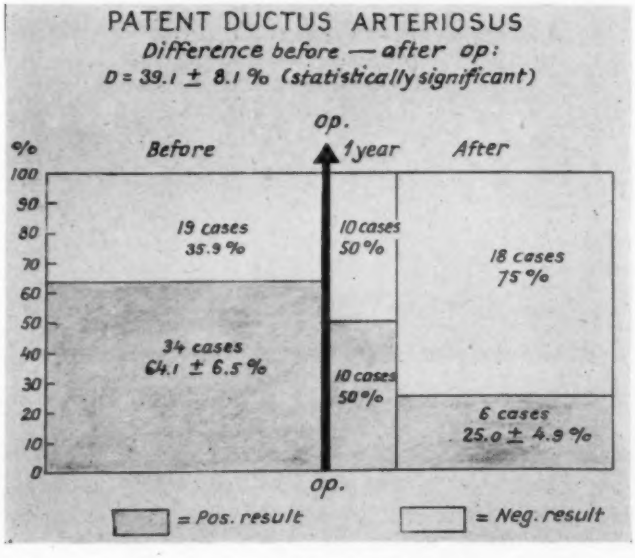


Fig. 6.—Patent ductus arteriosus. Patients examined before and after operation.

sized especially by Carlgren,[3] that there is a connection between gallop rhythm and myocardial damage. Finally, there is a group of twenty-two miscellaneous cases, in which 72.7 per cent of the tests were negative.

Fig. 3 presents electrocardiograms in a normal case with negative result of the hypoxia tolerance test, 9 per cent oxygen having been given for a period of ten minutes. Fig. 4 illustrates a case of acute myocarditis with positive hypoxia test. The patient was a 9-year-old boy with fatigue, pallor, enlargement of the left ventricle on x-ray, a slight systolic murmur, and a third sound gallop rhythm, phonocardiographically verified. The electrocardiogram was normal. Two months later the hypoxia test was negative, and the patient no longer showed any cardiac symptoms.

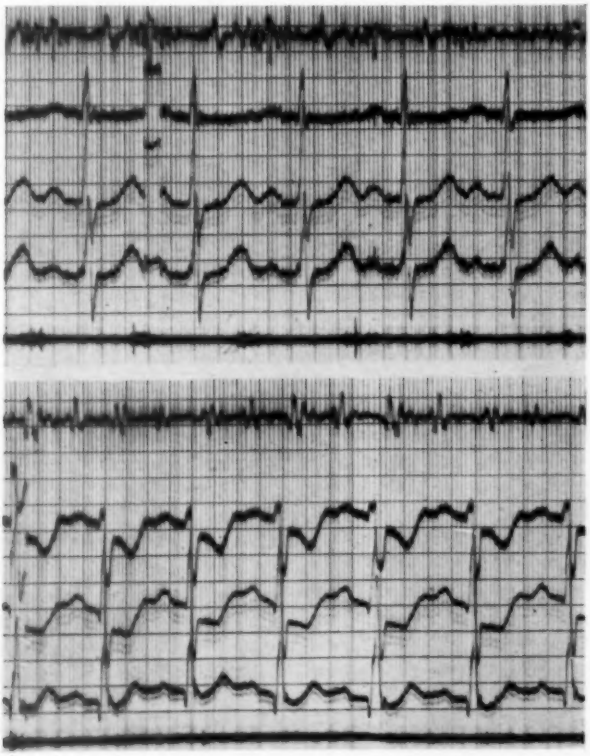

Fig. 7.—Three-year-old girl with patent ductus arteriosus; before operation. Positive result of hypoxia tolerance test.

The studies made in congenital heart disease are brought together in Figs. 5 and 6. Fig. 5 shows eighty cases of heart defects without cyanosis, fifty-three of which are patent ductus arteriosus, and twenty cases of cyanosis. It can be seen that two-thirds of the cases of acyanotic congenital defects which are not

patent ductus, perhaps mostly septal defects, react negatively. However, this group has hitherto not been systematically tested. Therefore it is necessary to wait until more experience is available.

The hypoxia test in "blue babies" has its own history. Most of these patients are small children in a delicate condition. Consequently we began to test them very carefully. At first we gave them 15 per cent oxygen, with no

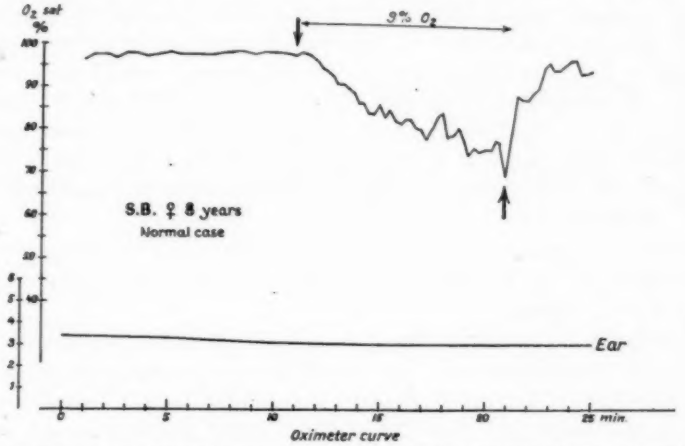


Fig. 8.—Oximeter curve. Arterial oxygen saturation during the hypoxia test in a normal patient.

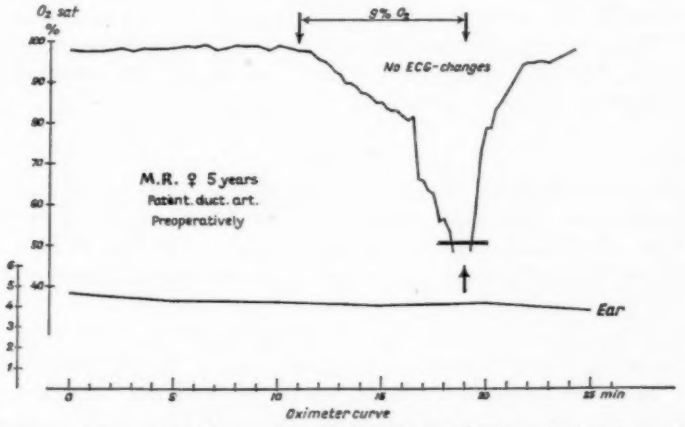


Fig. 9.—Oximeter curve. Arterial oxygen saturation during the hypoxia test in a 5-year-old girl with patent ductus arteriosus.

reaction. Some days later we tried 13 per cent, later 11, 10, and finally 9 per cent oxygen. The results were completely negative with no reaction at all. There was no shortness of breath and no marked increase in cyanosis. We then gave 8 and 7 per cent oxygen, a concentration which healthy children have

marked difficulties in tolerating. The same result—no reaction. This fact must signify that the organism in a case of permanent cyanosis is used to the lack of oxygen to such a degree that the normal reflex does not function. It would be of the greatest interest if the "blue babies" reacted positively to the hypoxia test some time after the Blalock-Taussig operation. The time after operation has until now been too short to judge the situation.*

Fig. 6 presents the data on patent ductus arteriosus. Before operation 64.1 per cent gave a positive test. The patients examined more than one year after operation showed quite another result. Only 25 per cent reacted positively. This difference is statistically significant. The twenty patients examined during the first year after the ligation of the ductus take an intermediate position, 50 per cent showing negative and 50 per cent positive reactions. This result illustrates both the improvements made by the operation and the value of the hypoxia tolerance test.

Fig. 7 is recorded from a 3-year-old girl. This was a typical case of patent ductus arteriosus. Before operation she reacted positively to the hypoxia test, as shown by the tracings.

In a few cases we have followed the oxygen saturation during the hypoxia test by means of an oximeter. Figs. 8 and 9 show the tracing obtained in one normal case and in one case of patent ductus arteriosus. The oxygen saturation of the arterial blood falls from 100 to about 70 per cent in a normal child. In the patent ductus patient the oxygen saturation fell much more, in fact so far down that the lowest point could not be determined on the scale. It is of special interest that in this patent ductus case, that of a girl of 5 years, there were no positive signs in the electrocardiogram or the phonocardiogram during the hypoxia test. Further studies in this field will show if this observation is in accordance with a rule or is an exception.

## SUMMARY

The hypoxia tolerance test has now been performed in 365 cases with about 600 examinations. In normal cases the reactions are negative with very few exceptions. Active rheumatic carditis and active myocarditis of other etiology give positive results in about three-quarters of the cases. Healed carditis and gallop rhythm give a positive result only in about 25 per cent.

In congenital heart disease, the patent ductus cases as a rule react positively before operation and negatively after the ligation. A few patients were also studied by means of the oximeter during the hypoxia test, making it possible to increase the value of the method. However, more cases must be examined.

Finally, there seems to be no doubt that patients with congenital heart defects and cyanosis do not react at all to the hypoxia tolerance test. This must signify that a child with permanent cyanosis is acclimated to the lack of oxygen and that he is unable to react in a customary way.

*Sixteen patients have, until now, been operated upon in Stockholm (six deaths).

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# CONGENITAL TOXOPLASMOSIS

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ALTHOUGH toxoplasmosis has not been frequently reported in human beings, it has recently been brought more to the forefront because of increasing interest in the disease and improved diagnostic methods.

This protozoan parasite was first observed in 1908 by Nicolle and Manceaux[1] and by Splendore.[2] It has been characterized[3, 4] by a world-wide geographical distribution, a pathogenicity for numerous hosts including mammals and birds, and an affinity for many tissues but especially those of the central nervous system. It is crescentic or curved, measures 4 to 7 $\mu$ in length and 2 to 3 $\mu$ in width, is pointed at one or both ends, and consists of cytoplasm with a rounded chromatin body situated centrally or nearer the blunter extremity. The toxoplasma[5] is larger and more curved than the encephalitozoon with which it may be confused,[6] and, unlike the encephalitozoon, is destroyed by freezing, stains deeply with hematoxylin-eosin, has poorly defined individual forms and produces a marked necrotizing reaction, which in the central nervous system is often followed by calcification. In addition, the toxoplasma may at times have to be differentiated[7] from other protozoan parasites such as the Leishmania and that causing avian malaria.

Although the cases reported by Janku[8] in 1923, Torres[9] in 1927, and Richter[9] in 1936 were later classified as probably being of the toxoplasmic group, there was no conclusive report of the parasite's causing disease in human beings until 1939 when Wolf, Cowen, and Paige[4] proved by transmission of toxoplasmosis to a large number of animals that the parasites found in the granulomatous lesions of a 31-day-old infant who died of widespread encephalomyelitis were of the toxoplasmic group.

Following their report of infantile toxoplasmosis, others discovered it to be the cause of an acute encephalitis in older children[3] and of a predominantly pulmonary infection in adults.[10, 11]

More reports[7, 12-24] on the infantile type followed, and with further study it was revealed[14-16, 23] that despite the severity of the disease many patients survived.

By 1946 Pratt-Thomas and Cannon[24] had found twenty-one cases of toxoplasmosis proved by autopsy, fifteen of which were in infants, while Callahan, Russell, and Smith[7] reported on a total of eighteen infantile cases that had had pathologic study; they did not include the case of Pratt-Thomas and Cannon, however. In February, 1947, Miller[23] had found a total of thirty-eight cases and added one of his own to the records.

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From the Pediatric Service of the New York Medical College and Flower-Fifth Avenue Hospitals, Dr. Reuel A. Benson, Director.

This case was presented before the Pediatric Section of the New York Academy of Medicine on May 8, 1947.

It is believed[3, 7, 25] that toxoplasmosis is transmitted to man from a reservoir in lower animals, many of which are domestic. However, in consideration of the positive neutralizing antibodies found in mothers of infants with the disease, it can be assumed that infantile toxoplasmosis can be acquired in utero[7, 12, 16, 19, 25-27] and that the toxoplasma[21, 28] probably crosses the placental barrier to infect the fetus. That this is very possible is illustrated by one patient[27] with chronic toxoplasmosis in whom each of three pregnancies activated a quiescent chorioretinal lesion, thus bringing up the probability that pregnancy has been an activating factor in some cases of the disease. The final proof of intrauterine transmission would be the finding of toxoplasma in the placenta, but no such verification has been forthcoming up to the present.

However, there is also the possibility that some cases may be acquired post partum since Zuelzer[19] reported one case in which the mother's serum did not reveal any neutralizing antibodies.

The outcome in toxoplasmosis may well depend upon the state of development of the fetus at the time of infection or the number of parasites invading the area, but the clinical course[7] depends upon the localization of the lesions. Therefore, variants may range from no findings[27] to those of the typical case. Some report cases in which no symptoms or signs were ever manifested but in which evidence of the parasite was revealed at necropsy[29] or through neutralizing antibody tests.[16, 21, 23, 27, 30, 31] Others[25, 27, 32] reveal cases in which only the eyes were involved, and in some cases[3] only systemic manifestations were noted. In the cases of human toxoplasmosis reported on to date, there has been noted[3] some involvement of the central nervous system with or without lesions in other organs. Furthermore, it is possible that some patients survive infections without important handicaps even if the infection involves the brain and eyes, and there is a probability that a fair number suffer cerebral damage without calcification.

In the typical case, the following criteria[3, 12, 14, 25] have been listed as necessary for the diagnosis of the infantile type of toxoplasmosis:

1. Infection occurring in utero or shortly after birth with symptoms present at birth or shortly thereafter.
2. Signs of cerebral injury, such as
   a. Tremors, spastic contractions of extremities, and convulsions;
   b. Microcephalus or internal hydrocephalus which is clinically evident or demonstrable by pneumoencephalography. The hydrocephalus in 80 per cent of cases is obstructive in type and progressive.
   c. Mental retardation, which may be present but is not essential, as shown by reports[16, 21] of some cases in which the intelligence was not affected.
3. Ocular signs such as ocular palsies, microphthalmus, enophthalmos, membranous masses of granulation tissue in the vitreous, and chorioretinitis, especially in the macular region, which consists of slightly depressed or elevated, white or reddish brown, round or oval patches with irregular, spotty black pigmentation. The lesions[7] visible by ophthalmoscopic examination are mainly bilateral and often multiple.

4. Roentgenographic evidence of intracerebral calcification of the irregularly distributed granulomata, which are often bilateral and involve the cerebral cortex and basal ganglia.

5. Xanthochromia, round cell pleocytosis, and high protein content of cerebrospinal fluid, plus the presence of toxoplasma on smear.

6. Recovery of toxoplasma from body fluids, especially from blood or cerebrospinal fluid, by direct smear or by inoculation of mice, rabbits, or both, intracerebrally and intraperitoneally.

7. Demonstration of toxoplasma neutralizing antibodies in the blood of infant or mother as described in the literature.[27, 30, 31]

Other pertinent findings may be:

1. Neonatal jaundice, which occasionally lasts many weeks and may be due to liver damage[15];

2. Hepatosplenomegaly, which lasts for many months;

3. Interstitial pneumonitis, which has been found in three cases[7];

4. Occasional anemia and leucopenia with absolute rise in lymphocytes;

5. Variable temperature, which may go from subnormal to elevated.

6. Gastrointestinal symptoms, such as vomiting and diarrhea, which may be initial symptoms of the disease;

7. Myocarditis, which was found at autopsy[7] in six cases but was not associated with clinical symptoms.

A complement fixation test is being studied but is not yet sufficiently developed to be useful for diagnosis.

The autopsy findings[3, 4, 12, 13, 24, 23] in typical cases have revealed focal areas of inflammation and necrosis and disseminated miliary granulomas which showed a marked tendency to calcify.

No effective therapy[25] has been devised to date. Sulfathiazole and sulfapyridine have shown promise in experimental toxoplasmosis but have not been tried in human cases. Penicillin[33] has been found to be ineffective for this type of infection.

Because of the relative rarity of cases of toxoplasmosis and because of the increasing importance of toxoplasma as an etiological factor, it was felt wise to stress the condition by reporting another case.

## CASE REPORT

I. L., a 17-month-old Negro female infant was admitted on Dec. 11, 1946, for observation because of loss of weight and mental retardation.

The infant had been full term, and delivery was spontaneous at a local hospital on July 14, 1945, after two hours of labor. The birth weight was 6 pounds and 4 ounces, and on discharge a diagnosis of microcephaly was made.

The family history was essentially negative. All siblings were alive and well. The mother was gravida iii, para iii, and had not had any evidence of illness during her pregnancy.

The baby failed to develop normally both physically and mentally and was referred to the hospital for further study.

On admission, her height was 59 cm. (23¼ inches), her weight 2.7 kg. (6 pounds), and she could neither hold up her head nor sit up. There was generalized spasticity including the neck, back, and all extremities (see Fig. 1). She had a weak cry and appeared

TABLE I. LABORATORY DATA

| | DECEMBER | | JANUARY | | MARCH | APRIL | JUNE |
|---|---|---|---|---|---|---|---|
| | 12 | 16 | 15 | 22 | 28 | 11 | 4 |
| Ieteric index | | 5 | 4 | 5 | 4 | | 5 |
| Van den Bergh | | Neg. | Neg. | Neg. | Neg. | | Neg. |
| Cephalin flocculation | | Neg. | Neg. | Neg. | Neg. | | Neg. |
| Phosphorus | | 3.5 | 3.3 | 4.5 | 3.6 | | 4.8 |
| Phosphatase | | 2.0 | 4.6 | 4.0 | 6.8 | | 10.3 |
| Total cholesterol | | 346 | 188 | 224 | 248 | | 330 |
| Free cholesterol | | 108 | 39 | 51 | 67 | | 92 |
| Cholesterol esters | | 238 | 149 | 173 | 181 | | 238 |
| Total serum protein | 6 | 6.2 | 7.3 | 7.6 | 7.3 | | 8.1 |
| Albumin | | 4.3 | 4.7 | 5.6 | 4.5 | | 5.4 |
| Globulin | | 2.9 | 2.6 | 2.6 | 2.8 | | 2.7 |
| A/G ratio | | 1.5 | 1.8 | 1.9 | 1.6 | | 2.0 |
| RBC (in millions) | | 7 | 5.37 | | 4.91 | | |
| Hemoglobin | | 9 | 9 | | 9.4 | | |
| WBC (in thousands) | | 12 | 9.25 | | 9.2 | | 9.75 |
| Lymphocytes | | 82 | 63 | | 60 | | 61 |
| Polynuclears | | 12 | 27 | | 27 | | 39 |
| Mononuclears | | 4 | 8 | | 1 | | |
| Eosinophiles | | 2 | 2 | | 2 | | |
| $CO_2$ combining power | 37 | | | | 48 | | |
| Wassermann (baby) | Neg. | | | | | | |
| Wassermann (mother) | | | Neg. | | | | |
| Creatinine | | | | | 1.3 | | |
| Urea nitrogen | | | | | 15 | | |
| Rose-Exton test | | | | | | | |
| Fasting sugar | | | | | 110 | | |
| ½ hour after 5 Gm. glucose | | | | | 130 | | |
| 1 hour after 10 Gm. glucose | | | | | 155 | | |
| Spinal fluid | | | | | | | |
| Color | | Clear | | | Clear | | |
| Pressure | | 170 mm. | | | Normal | | |
| Cells | | 0 | | | 2 | | |
| Sugar | | 72 | | | 55 | | |
| Proteins | | 43 | | | 38 | | |
| Chlorides | | 713 | | | 704 | | |
| X-rays | | | | | | | |
| Skull | | Multiple Calcified Areas | | | | | |
| Long bones | | Normal | | | | | |
| Chest | | | | | | Neg. | |
| Weil-Felix | | | Neg. | | | | |
| Widal | | | Neg. | | | | |
| Heterophile | | | | | | 1:32 | |
| Urine | | | | | | | |
| Albumin | | | | | + | Neg. | |
| Sugar | | | | | + | Neg. | |
| Hyaline casts | | | | | Occ. | Neg. | |
| Pitressin test | | | | | Neg. | Neg. | |

TABLE II. HEIGHT AND WEIGHT PROGRESS

| | DEC. 11 | JAN. 5 | MARCH 25 | APRIL 21 | JUNE 4 |
|---|---|---|---|---|---|
| Length (cm.) | | 59 | 59.4 | 60.6 | 62.5 |
| Head to pubis | | 34 | 35 | 35.6 | 37.5 |
| Pubis to heel | | 25 | 24.4 | 25 | 25 |
| Chest (cm.) | | 40 | 43.8 | 43.8 | 45.0 |
| Abdomen (cm.) | | 37 | 41.3 | 41.3 | 41.3 |
| Occipitofrontal circumference | | 34 | 36.3 | 36.3 | 36.3 |
| Weight (kg.) | 2.7 | | 5.6 | 5.7 | 6.5 |

marasmic. The mucous membranes were dry as was the skin, which was also scaly and hung in loose folds. The hands and feet were swollen and bright pink in color.

The head was microcephalic with the occipitofrontal circumference measuring 34 cm. (13¼ inches), and all the fontanels were closed. There was a rotary nystagmoid movement of the eyes, a high arched palate, and only one upper and two lower central incisors had erupted.

The heart, lungs, and abdomen did not reveal any abnormalities.

Blood Wassermann tests done on the baby and her mother were negative, and both of them were Rh positive, Type 0.

Fig. 1.—Sitting position, revealing marked spasticity and microcephaly.

Weil-Felix, Widal, and brucellosis tests were negative, while the heterophile antibody reaction was positive only in 1:32 dilution.

A blood count on December 18 revealed an anemia, polycythemia and lymphocytic leucocytosis, but by January 8, the blood count was markedly improved and continued so. Total serum proteins at first were low and the total cholesterol high, but when repeated on January 15 and 22 they had become normal.

A spinal tap done on Dec. 16, 1946, revealed clear fluid, no increase of pressure, no cells, protein 43 mg., sugar 72 mg., and chlorides 713 mg.

On Dec. 17, 1946, an x-ray of the skull revealed diffuse areas of calcification (Fig. 2), at which time a tentative diagnosis of toxoplasmosis was made. X-rays for bone age and pathologic conditions of the chest did not reveal any abnormalities. On December 18, the ophthalmologist reported diffuse bilateral chorioretinitis on fundus examination.

In view of these findings, blood was obtained for inoculation into mice and rabbits, but no toxoplasma was found. Spinal fluid was also injected into these animals, but again no evidence of the parasite was detected. Neutralizing antibody tests* done on the infant's blood were negative.

*The neutralizing antibody tests were done through the courtesy of Dr. D. Cowen of the Medical Center, New York City.

During her stay in the hospital, the baby improved, her weight increasing from 2.7 kg. (6 pounds) to 6.5 kg. (14 pounds) and her height from 59 cm. (23¼ inches) to 62.5 cm. (25 inches). (See Tables I and II.)

Fig. 2.—X-ray of skull. Note multiple intracerebral calcifications.

## DISCUSSION

Although most of the cases reported have occurred in the white race, this is the third case found in the Negro race, two others[12, 19] having been reported previously.

Up to the present time, more females have been affected than males. However, as pointed out by another writer,[7] the cases are too few as yet to consider that sex plays any part in the picture.

In the case presented here the essential clinical features listed as necessary for the diagnosis of infantile toxoplasmosis were present, namely:

1. Microcephalus,
2. Chorioretinitis,
3. Diffuse cerebral calcification,
4. Mental deficiency.

Of the cases previously reported, only two[13] were recorded as microcephalic, and in two others[15, 23] the heads were slightly smaller than normal. The present case was definitely of the microcephalic type, and even at present the occipitofrontal circumference is only about two-thirds of normal size.

An unusual feature noted in this case was the marked longitudinal shortening, with the height on admission being the equivalent of that of a 3-month-old infant. Even now it is only about two-thirds normal. Since the dwarfism is of the uniform type, it can be surmised that the pituitary may have been involved in the process with the generalized shortening as a result. In substantiation of this is the fact that moderate atrophy of the sella turcica[13] has been noted in one previous case.

Regarding the inability to isolate the parasite from the blood or spinal fluid, it must be remembered[25] that in some older infants and children the toxoplasma may still be present and active, but in many cases the lesions may represent only the residual of a previous infection which has subsided. As a matter of fact, Sabin[3] reported negative results when he inoculated mice with spinal fluid and blood obtained on the tenth day of the disease, and in Miller's[23] case also no parasite was found in the spinal fluid.

Concerning the neutralizing antibodies, writers[3, 14, 32] have found that these antibodies disappear as early as the sixth week after the infection, and therefore the optimum time for taking the test would be in the first three to four weeks after the onset of the disease. Moreover, while a positive neutralizing antibody test is strong evidence in favor of toxoplasmic infection past or present, a negative result[34] does not eliminate the possibility of its having been present and subsided.

However, since our patient manifested all the clinical criteria necessary, it can be assumed that this was a typical case of toxoplasmosis.

## SUMMARY AND CONCLUSION

1. A case of congenital toxoplasmosis in a 17-month-old Negro female infant is reported.

2. Microcephalus, chorioretinitis, diffuse cerebral calcification, and mental deficiency were all present.

3. Dwarfism was noted for the first time in this condition.

4. In late cases toxoplasma may not be isolated.

5. A negative neutralizing antibody test after the fourth week of illness does not nullify the diagnosis.

6. The discovery of toxoplasma as a cause of mental deficiency and encephalomyelitis adds another causative agent to be considered in these conditions. Furthermore, since cases of toxoplasmosis arise as a result of placental transmission, prophylaxis would depend upon the early diagnosis of the condition in the pregnant mother. Following its diagnosis, an effective method of destroying the parasite must be found. Since the number of reports of the infection are increasing as it is better understood and being watched for, it is of the utmost importance to endeavor to prevent its occurrence in infants through early detection in the mother.

Therefore the problem presenting itself is that of devising a simple diagnostic test and also of securing an effective therapy to eliminate the infection before it has produced permanent changes.

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# THE TREATMENT OF TUBERCULOUS MENINGITIS

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IN 1945, Feldman and Hinshaw[1] showed that streptomycin suppressed tuberculosis in guinea pigs, and experiments on human beings seemed to show similar effects.[2] Since that time, streptomycin has been used for all types of tuberculosis and found to be of definite value as an adjuvant treatment for acute miliary tuberculosis, tuberculous meningitis, and prior to operations on tuberculous chests.

Its use in miliary tuberculosis is hopeful.[3] Early, fine tuberculous lesions respond much more favorably than do older fibrocaseous lesions.[4] Hinshaw and his associates[5] treated twelve patients with miliary tuberculosis and tuberculous meningitis. Six patients expired; five patients survived from two to ten months. Symptomatic response was observed after one to two weeks of therapy, and in certain cases there was clinical, roentgenographic, and histopathologic evidence of healing, but there were no actual cures. All patients treated continued to show slight abnormalities in the spinal fluid, such as an elevation of protein and cells at the time of discontinuance of the drug. It has been further shown[6] that streptomycin has only a suppressive, inhibitory action on tuberculosis with a tendency to recurrence of symptoms following termination of treatment.

Our paper includes the reports of nine patients ill with tuberculous meningitis, who were treated with streptomycin. Marked improvement was obtained in two individuals, but the eventual outcome is not known. The protocols of these nine cases are as follows:

## CASE REPORTS

CASE 1.—C. P., a 4-year-old white girl, was admitted to the Department of Contagious Diseases of City Hospital on Dec. 19, 1946, acutely and seriously ill. The illness dated back to September, 1946, when the child became anorexic, slept poorly at night, was restless, and failed to gain weight. This continued until December, 1946, when the malaise became prominent, she did not play normally, and the anorexia became pronounced. On December 8, a cough and a slight fever occurred. By December 11, the cough was worse and a temperature of 38° to 39° C. was noted. These symptoms remained unchanged until December 16, when the respirations became rapid. On December 19, meningitis was recognized, and she was admitted to the hospital.

The child had always been well except for measles at 3 months of age and pertussis at 2 years of age. During the previous year, she had occasionally stayed with an aunt who had a chronic cough supposedly due to carcinoma of the lung and who died shortly before the patient became ill.

Physical examination revealed a well-developed but poorly nourished white girl. She was lethargic, had cyanosis of the lips and finger tips, and her face had a dusky, pale appearance. She was acutely ill. The temperature was 38.9° C.; pulse 110; respirations rapid and shallow, 60 per minute, with

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occasional grunting and a hacking cough. Fine moist râles were heard throughout the right chest with no discernible dulness; the left chest was clear to percussion and auscultation. The abdomen was tender throughout, and the spleen was palpated two fingerbreadths below the left costal margin. The neck was rigid to anterior flexion, and the Kernig sign was positive. Examination of the blood disclosed 15.0 Gm. of hemoglobin, a red blood cell count of 4.30 million, and a white blood cell count of 10,600 with 83 per cent polymorphonuclears and 17 per cent lymphocytes. The urine was normal. A lumbar puncture revealed clear cerebrospinal fluid containing 36 cells, 96 per cent lymphocytes and 4 per cent polymorphonuclears, and a four plus reaction to the Pandy test. The protein was 80 mg. per 100 c.c.; sugar 30 mg. per 100 c.c.; chloride 423 mg. and sodium chloride 699 mg. per 100 c.c. The qualitative five-tube sugar test showed no reduction in any of the five tubes.

X-ray examination of the chest revealed numerous minute, soft, discrete nodulations throughout both lung fields consistent with a diagnosis of diffuse, hematogenous, pulmonary tuberculosis.

A diagnosis of acute, diffuse, hematogenous tuberculosis with tuberculous meningitis was made, and the patient was given daily 1.2 Gm. of streptomycin intramuscularly in divided doses along with 5.0 Gm. of Promin intramuscularly.

During the first week, the patient was in a precarious condition. The temperature fluctuated between 38.5° and 40.0° C.; the pulse and respirations were elevated. She remained cyanotic, ate poorly, and continued to lose weight. On the fourteenth hospital day, slight distention of the abdomen was found. The abdomen was doughy, and no fluid wave was demonstrable. The examiners thought that she now showed clinical evidence of tuberculous peritonitis.

A repeat x-ray examination of the chest about this time showed no significant change in the pulmonary disease since the initial examination. Throughout the early weeks, the patient continued to have cyanosis and was very inactive, refusing to sit up or play with her toys. Food and fluids were taken poorly, necessitating parenteral fluids to meet the daily requirements. The temperature began to fall slightly, after three weeks, to 38° C., but the pulse remained rapid, 110 per minute, and the respirations remained at from 50 to 60 per minute. There was no significant change in the cerebrospinal fluid.

During the subsequent four weeks, progressive improvement was noted. The temperature, pulse, and respirations returned to normal and remained so. Radiographs of the chest showed progressive diminution in the density of the pulmonary lesions. The cerebrospinal fluid sugar and chlorides began to rise to the normal range, but there was still an increase in the amount of protein and cells. Cyanosis was less marked, and the child became more active, showing much more interest in her surroundings. Her appetite increased, although her weight remained stabilized.

About the seventh week, the patient was markedly improved clinically. The abdominal distention had receded; the cyanosis had completely disappeared; the neck was no longer stiff; and the chest was clear to physical examination. Food and fluids were taken well. The weight which had decreased about four pounds during her illness began to return slowly. Promin was discontinued on the sixtieth hospital day and streptomycin was continued.

For the remaining twelve weeks, there was an uneventful course. Films of the chest continued to show clearing of the nodular shadows. There were no signs of mental retardation. The temperature, the pulse, and the respirations remained normal, and on the one hundred thirty-fourth hospital day, streptomycin, a total of 159.2 Gm. of which had been administered, was discontinued. For three weeks following, the patient was closely observed for changes in her condition, and since none was noted and the chest film showed complete clearing

of the miliary shadows (although the cerebrospinal fluid still contained 28 cells, all of which were lymphocytes, and 55 mg. of protein), she was discharged on the one hundred fifty-third hospital day.

Spinal fluid and gastric washings obtained on admission were inoculated into guinea pigs. The animal inoculated with the gastric washings died several days later and no conclusion was obtained, but the one inoculated with the spinal fluid was sacrificed after six weeks and found to have diffuse tuberculous lesions from which the tubercle bacillus was recovered.

The patient was followed at weekly intervals subsequently, and she continued to show improvement in weight, appearance, and activity for three weeks. During the fourth week, however, fever and anorexia were noted, and the patient was readmitted to the hospital on June 25, 1947.

This time the spinal fluid contained 330 cells, 100 per cent of which were lymphocytes; the protein was 180 mg. per 100 c.c.; the chlorides and the sugar content were within normal limits. The temperature was 39° C., and the patient appeared lethargic and chronically ill.

X-ray examination showed complete resolution of the previous pulmonary infiltration.

Streptomycin was again administered, and the dose was raised to 3 Gm. per day in divided doses. Her general condition has remained poor, and at the present writing, the sixty-second hospital day of the patient's second admission, the temperature still fluctuates between 37° and 38° C. The present cerebrospinal fluid shows an increase in cells (850 lymphocytes) and protein (280 mg.) despite continued therapy. (She died on Dec. 18, 1947.)

CASE 2.—J. N., an 18-month-old white, male infant, was well until the latter part of October, 1946, when he had a fever and cough which were treated as acute bronchitis. He recovered promptly and remained well until Feb. 13, 1947, when he had a second attack of fever with a cough. Restlessness and irritability were noted, the child cried continuously, and he slept poorly at night. He was treated with sulfadiazine without result. On February 15, he became listless and lethargic, refused feedings, and developed a stiff neck. On the following day symptoms continued unabated, and he was admitted to the hospital.

Physical examination revealed an acutely ill, lethargic, and dehydrated infant lying in an opisthotonic position. The temperature was 38.5° C., the pulse 120, and the respirations 88. There was marked nuchal rigidity. Respirations were rapid and shallow and out of proportion to the fever, but there was no cyanosis or dulness to percussion. Occasional râles were heard at the right base, posteriorly. The Kernig and Brudzinski signs were positive.

Lumbar puncture was performed, yielding slightly cloudy spinal fluid containing 520 cells with 95 per cent lymphocytes and 4 per cent polymorphonuclears. The Pandy test was four plus. The protein content was 300 mg. per 100 c.c., sugar 25 mg. per cent, and sodium chloride 673 mg. per cent. Direct smear of the fluid showed acid-fast organisms identified morphologically as *Mycobacterium tuberculosis*.

X-ray examination of the chest showed dense, mottled infiltrations extending from the hilus to the bases bilaterally with tiny nodular shadows scattered throughout the lung fields, consistent with the diagnosis of miliary tuberculosis.

A diagnosis of miliary tuberculosis with tuberculous meningitis was made, and daily streptomycin therapy was instituted. One gram of streptomycin intramuscularly and one gram of promin intravenously were given.

A tuberculin test made on admission with old tuberculin, 1:1,000 dilution, was negative. When repeated four days later with 1:100 dilution, the reaction was faintly positive.

During the first two weeks of treatment, the patient did poorly. The fever fluctuated to 39° C. daily, the pulse rate ranged from 100 to 130 per minute, and respirations remained about 30 to 40 per minute. He remained in an opisthotonic position continually, had a high shrieking cry, and developed a divergent strabismus of the right eye. The eye grounds were normal, but the child complained that the "lights were out." He fumbled for his toys and bottle, as if blind, and beginning hydrocephalus was suspected. Pneumoencephalograms were performed which showed air in the basal cisterns, but no air was visualized in the ventricles, possibly due to blockage in the region of the fourth ventricle. By the fifth hospital week, the temperature began to stabilize, rising only to 37.8° C. daily; the respirations became normal but the pulse rate remained rapid, ranging from about 110 to 120 per minute. Cerebrospinal fluid findings showed definite improvement with a decrease in number of cells (50) and a rise in sugar (52 mg.) and chlorides (426 mg. of chloride and 704 mg. of sodium chloride).

The patient continued to improve as evidenced both clinically and roentgenologically. Follow-up films of the chest showed gradual progressive resolution of the mottled infiltrations in the lungs. Promin was discontinued on the sixty-ninth hospital day, but streptomycin was not discontinued until the eighty-seventh hospital day. At that time, the spinal fluid still contained 43 lymphocytes. The proteins were 120 mg. per 100 c.c., sugar 67 mg. per 100 c.c., chlorides 439 mg., and sodium chloride 724 mg. The temperature, the pulse, and the respirations remained normal, and the baby seemed to be markedly improved. He ate well and gained about four pounds. The eye grounds failed to show tubercles, optic atrophy, or papilledema, but vision was still diminished. The patient was more active and played with his toys, and his appetite was good. No obvious mental deterioration was noted, and the child's vocabulary increased steadily in keeping with his age.

The patient remained in the hospital for fifty days after the discontinuance of streptomycin and continued to show a good clinical response. He seemed to be alert mentally and appeared healthy and happy. He had gained the weight he lost in the early period of his illness and weighed 30 pounds at the time of discharge. Vision did not return, and light perception was all that remained. The spinal fluid continued to show a slight increase in proteins and cells. His hearing was good, and there was no evidence of vestibular damage. The patient was discharged markedly improved on the one hundred thirty-first hospital day, having received a total of 86 Gm. of streptomycin, but the prognosis is still guarded.

CASE 3.—C. W., a 9-year-old white boy, was apparently well until April 26, 1947, when he began to complain of intermittent headaches and anorexia. On May 1, he had malaise, became nauseated and vomited, and had a temperature of 39° C. On May 3, his temperature varied from 39° to 39.5° C., and he received penicillin. For the next several days, he became increasingly lethargic and his headache more severe. On May 8, he attended school but was sent home because of drowsiness. Three days later, he became delirious, sweated profusely, was very lethargic, and was admitted to the Department of Contagious Diseases. There was no known exposure to tuberculosis.

On physical examination, the temperature was 38.5 C., pulse 150 per minute, and respirations 35 per minute. The patient was a well-developed, well-nourished boy, who was semicomatose but responded to noxious stimuli. The neck was stiff and resisted anterior flexions, positive Kernig and Brudzinski signs were present, and the chest was clear to percussion and auscultation. The remainder of the physical examination was negative.

The cerebrospinal fluid had normal dynamics. It contained 342 cells, 50 per cent of which were lymphocytes and 50 per cent polymorphonuclears; the reaction to the Pandy test was four plus; proteins were 360 mg. per 100 c.c., sugar 46 mg., chlorides 371 mg., and sodium chloride 612 mg.

X-ray examination of the chest showed no evidence of pulmonary infiltration. The patient was given one gram of streptomycin intramuscularly daily in divided doses.

A tuberculin test with old tuberculin (1:1,000 dilution) was very strongly positive.

The patient remained in critical condition throughout his hospital stay. The coma deepened and he showed increasing, generalized muscular spasticity. His arms remained stiff at his sides and resisted bending; the hands remained clenched and flexed sharply at the wrists. The legs also showed an increase of muscle tone, and the feet were held in forcible plantar flexion. Reflexes were all normal.

Streptomycin was continued for six weeks without clinical improvement. Repeat films of the chest showed prominent hilar markings which were thought to represent a tuberculous process, but no pulmonary infiltration was present.

Cerebrospinal fluid continued to show an elevation in cells (264, with 85 per cent lymphocytes and 15 per cent polymorphonuclears). Spinal fluid proteins had risen to 1,440 mg. per 100 c.c., and chlorides remained low (405 mg. as chloride and 668 mg. of sodium chloride).

Although streptomycin was continued, the child's condition gradually became worse. The temperature remained about 40° C., and the patient finally expired on the fifty-first hospital day.

Guinea pigs inoculated with spinal fluid were sacrificed, and *Myco. tuberculosis* was identified in the lymph glands.

Autopsy revealed multiple tuberculous foci throughout the meninges and brain.

CASE 4.—On May 7, 1947, B. W., a 3-year-old Negro boy, had fever and was restless and irritable. He continued to have a daily rise in temperature, particularly in the evening. By May 21, he began to cough, and his attending physician made a cutaneous tuberculin test, which was negative. On May 24, the child vomited, and the mother noticed that the left eyelid drooped. Vomiting, fever, and irritability continued, and on May 28 he was admitted to the hospital.

Physical examination revealed the temperature to be 37.6° C., the pulse 52, and the respirations 36 per minute. The patient appeared acutely ill and very irritable, and he assumed an opisthotonic position. There was ptosis of the left eyelid with bilateral edema of both lids, slight divergent strabismus of the left eye, and a serous discharge from the nose with a postnasal discharge. The neck was slightly resistant to anterior flexion; the abdomen was moderately distended, and the liver was palpated 2 cm. below the costal margin.

Lumbar puncture revealed clear fluid containing 13 cells, 80 per cent of which were lymphocytes. The reaction to the Pandy test was four plus. The protein level was 36 mg. per 100 c.c., the sugar 15 mg. per 100 c.c., and the chlorides 410 mg. per 100 c.c.

An x-ray examination of the chest showed numerous irregularly shaped areas of increased density throughout both lung fields, consistent with a diagnosis of diffuse, hematogenous tuberculosis.

A diagnosis of miliary tuberculosis with tuberculous meningitis was made, and streptomycin therapy was initiated. He received one gram of streptomycin intramuscularly daily.

The patient remained irritable, restless, and anorexic for several weeks, and the temperature had a spiking course, rising to 39.5° C. every afternoon. A repeat examination of the spinal fluid one week after streptomycin therapy was initiated showed no change in the findings except a rise in the sugar content to normal.

The guinea pig inoculation was positive.

By the third hospital week, the patient's condition was improved. The restlessness and the irritability diminished. The ptosis of the left eyelid disappeared and the strabismus diminished. The patient regained his appetite, but his weight remained unchanged.

By the seventh week of treatment, chest films began to show significant clearing of the miliary lesions in the lungs. Repeat examination of the cerebrospinal fluid showed 68 cells; protein was 130 mg., and chlorides were 445 mg. as chloride and 734 mg. as sodium chloride per 100 c.c.

At the present time, the temperature is still elevated to 38° C. and the blood sedimentation rate is 27 mm. in one hour. Although improvement has been shown clinically and roentgenologically with the use of streptomycin, the period of observation has been too short to draw any conclusions.

CASE 5.—J. C., a 19-year-old Negro boy, first became ill on April 2, 1947, when he began to have frontal headaches, a cough productive of small amounts of green sputum, and a slight fever. This lasted about one week.

In May, there was a recurrence of these symptoms of about the same duration, and on July 7, 1947, there was another episode of frontal headache, weakness, and fever plus constipation. The patient remained in bed nineteen days and finally returned to work. He had lost about 30 pounds of weight since April. In August, frontal headaches recurred and were located directly over both eyes. These were constant and were not relieved by aspirin. They continued unabated, becoming more intense, and on August 16, the temperature was 39° C. and he vomited. The vomiting and the headache continued, and two days later pain in the back of the neck was noted. This became more severe, and he was admitted to the medical department of City Hospital on Aug. 19, 1947.

Physical examination revealed a well-developed and poorly nourished Negro male, who appeared to be moderately ill and showed signs of recent weight loss. The temperature was 39.6° C., pulse 80, respirations 18, blood pressure 122/74. With the exception of a stiff neck, fever, and irritability, no abnormalities were found.

The lumbar puncture revealed clear fluid under normal pressure containing 217 cells, 80 per cent of which were lymphocytes and 20 per cent polymorphonuclears. The reaction to the Pandy test was one plus; protein was 65 mg. per 100 c.c., sugar 31 mg. per 100 c.c., chloride 470 mg., and sodium chloride 775 mg.

X-ray examination showed slight nodular infiltration in both apices and subapical regions, suggestive of bilateral minimal pulmonary tuberculosis.

The tuberculin test was positive in first-strength P.P.D. The diagnosis was pulmonary tuberculosis with tuberculous meningitis, and the patient was transferred to the Department of Contagious Diseases for streptomycin therapy. A dosage of 2 Gm. per day intramuscularly was started.

For the first week, the patient had an irregular temperature ranging from 38° to 41° C., which gradually changed to a daily spiking fever. The patient remained lucid and well oriented, but the headaches remained severe, enough so to require Demerol to control the pain. By the second week, the temperature had stabilized at 38.5° C. where it has remained to date. On three consecutive occasions, 100,000 units (0.1 Gm.) of streptomycin were given intra-

thecally and were well tolerated by the patient. This has had little effect on the cerebrospinal fluid as it continued to show an increase in cells and protein above the normal limits.

At the present time (Jan. 27, 1948), the patient seems to be doing well clinically. His headaches have subsided, his neck is no longer stiff, irritability has decreased, appetite has increased, and his mental status is good.

CASE 6.—H. P., a 35-year-old Negro man, had tuberculosis and silicosis for three years and was in a sanatorium from January, 1946, until April, 1947, when he left without permission. X-ray examination at that time showed fine, diffuse nodulations throughout both lung fields. He also developed renal tuberculosis and tuberculous epididymitis. The diagnosis was chronic miliary tuberculosis with renal tuberculosis and tuberculous epididymitis.

Following his voluntary release, he remained at home and seemed to do well until approximately two weeks before admission when he began to have headaches with chills and fever. One week before admission, he vomited and noticed a stiff neck. Although he remained lucid, he gradually became lethargic. On the day prior to admission he became confused, argumentative, and incoherent, and lethargy was pronounced. This continued unabated, and he was admitted May 17, 1947, to the Department of Contagious Diseases with tuberculous meningitis.

Physical examination revealed a fairly well-developed and poorly nourished male, who was very confused and disoriented. The temperature was 38° C., the pulse 80, and the respirations 22. The chest revealed dulness in the left axillary space; the breath sounds were vesicular throughout, but fine râles were heard throughout both lung fields. No areas of consolidation or cavitation could be determined. The neck was rigid to anterior flexion, Kernig and Brudzinski signs were positive, and no pathologic reflexes were obtained.

The urine was cloudy and contained three plus albumin, 5 to 6 white blood cells per high power field, and was loaded with granular casts. No red blood cells were present.

The cerebrospinal fluid was clear and contained 147 cells, 50 per cent of which were lymphocytes and 50 per cent polymorphonuclears; the Pandy test was four plus, Ross-Jones four plus, protein 90 mg., sugar 50 mg. per 100 c.c., 405 mg. of chloride, and sodium chloride 668 mg. No bacteria were seen.

X-ray examination of the chest showed multiple tiny nodular shadows throughout both lung fields, consistent with miliary pulmonary tuberculosis.

The patient was placed on daily doses of 2 Gm. of streptomycin intramuscularly. There was no noticeable improvement in his condition and, despite therapy, he remained in a critical condition with a fever ranging between 38° and 39° C. The mental confusion and the disorientation remained unchanged. Kernig and Brudzinski signs were consistently present, and after one month, the cerebrospinal fluid continued to show an abnormal increase in cells (240 cells, 100 per cent lymphocytes) and a protein content of 180 mg. per 100 c.c.

A total dose of 150 Gm. of streptomycin was administered, but at no time during the hospital course was improvement noted. On the seventy-ninth hospital day, the fever rose to 41° C. and the patient expired.

CASE 7.—G. B., an 18-year-old Negro boy, was admitted to the Department of Contagious Diseases on Nov. 6, 1946, having been transferred from another hospital with a diagnosis of tuberculous meningitis.

Three months prior to admission, the patient had become short of breath and had lost considerable weight. One month prior to admission, he had developed a cold with a cough which lasted for one week. Following this, he noticed pain in the left chest which increased on inspiration and seemed to "cut

off his breath." Twelve days before admission, he complained of frontal headache, fever, and vomiting and was taken to another hospital. While in the hospital, the patient's symptoms became progressively worse, and he finally became semicomatose and delirious. His eyes became crossed, the vomiting continued, and stiffness of the neck occurred. A lumbar puncture was performed, and he was transferred to the Contagious Department.

Physical examination revealed a poorly nourished Negro male, who was semicomatose, with a temperature of 39.5° C., a pulse rate of 160 per minute, and respirations of 32 per minute. The blood pressure was 150 systolic and 100 diastolic. The neck was rigid to anterior flexion. There was dullness at the right base posteriorly with decreased fremitus. There were positive Kernig and Brudzinski signs.

X-ray examination of the chest showed a dense homogeneous shadow at the right base extending upward along the right lateral chest wall consistent with pleural effusion. No pulmonary infiltration was present.

Lumbar puncture revealed slightly opalescent fluid under normal pressure, containing 78 cells (85 per cent lymphocytes and 15 per cent polymorphonuclears). The Pandy test was four plus. By direct smear, several organisms were seen and identified morphologically as *Myco. tuberculosis.* The cerebrospinal fluid protein was 180 mg., sugar 33 mg., chlorides 400 mg., and sodium chloride 668 mg.

Guinea pig injection was positive for tubercle bacillus.

The diagnosis was tuberculous pleurisy with effusion and tuberculous meningitis.

Four grams of streptomycin administered intramuscularly and 0.1 Gm. of streptomycin intrathecally were given daily, together with 5 Gm. of promin every four hours.

On the second hospital day, a thoracentesis of the right side was performed, and 50 c.c. of straw-colored fluid were obtained, free of bacteria and tubercle bacilli.

During the first three days of therapy, the temperature fell toward normal and the patient became more lucid. This was for a short period, however, for he gradually lapsed into coma by the eighth hospital day and expired on the twelfth hospital day, having received a total of 36.5 Gm. of streptomycin intramuscularly and 1.1 Gm. intrathecally. The total dose of promin was 200 Gm.

Case 8.—P. F., an 8-year-old white girl, was admitted to City Hospital on May 26, 1947, with a diagnosis of tuberculous meningitis.

The patient had been well until April 15 when she returned from school with a severe headache located behind both eyes. She also vomited. The vomiting and headache continued for several days, and she was admitted to another hospital, where x-rays and lumbar puncture were performed. A presumptive diagnosis of tuberculous meningitis was made and streptomycin initiated for five days. The exact dose was not obtainable. She seemed to respond well to treatment and was discharged six days later. While at home, she became progressively worse, having periods of mental confusion and vomiting, and on the evening of May 21, she began to have convulsions with rapid shaking movements of the arms and legs. This attack lasted several minutes and during the next few days was repeated many times. The patient finally lapsed into coma and was admitted to City Hospital.

Physical examination revealed a temperature of 38° C., pulse 120 per minute, respirations 22 per minute. The patient was an emaciated, weak, lethargic girl, who when aroused complained bitterly of generalized pains. Her neck was rigid, and Kernig and Brudzinski signs were positive. The remainder of the examination was negative.

Lumbar puncture revealed slightly cloudy spinal fluid containing 1,530 cells, 28 per cent of which were lymphocytes and 72 per cent polymorphonuclear cells. Protein was 178 mg. per 100 c.c.; sugar was 25 mg. per 100 c.c. *Myco. tuberculosis* was identified by direct smear from a pellicle by acid-fast stain.

X-ray examination of the chest revealed the presence of small, calcific, oval shadows in the periphery of both lung fields, which appeared to be healed tuberculous foci bilaterally.

The patient was immediately started on one gram of streptomycin intramuscularly in daily divided doses. The temperature remained elevated to 38.5° C., and the pulse rate ranged between 110 and 120 per minute throughout her hospital stay. She did not respond to therapy, the coma gradually deepened, and the respirations finally ceased. Despite stimulants and artificial respiration, the patient expired on the tenth hospital day. She had received 9.5 Gm. of streptomycin on this admission.

The findings at autopsy verified the diagnosis of tuberculous meningitis.

CASE 9.—J. B., a 13-year-old Negro boy, was admitted to the Department of Contagious Diseases on Aug. 29, 1947.

Three weeks prior to admission to the hospital, he began to complain of headaches and had malaise and fever. He became lethargic and remained at home. He did not play as usual. The headache was continuous, bilateral, and associated with neck pain. There was an afternoon rise in temperature each day. About two weeks prior to admission, he began to sleep all day. He had anorexia, and he became delirious on the day of admission. He was restless, dyspneic, and acutely ill with signs of meningeal irritation and some ptosis of the left eyelid.

Streptomycin therapy was started on September 4. He was given 2 million units of streptomycin intramuscularly, 1.5 Gm. of sulfadiazine, 5 c.c. of promin intravenously, and approximately 300,000 units of penicillin daily. He developed a right sixth nerve palsy on September 18. The patient's temperature the last forty hours mounted to 43° C. He expired on Sept. 21, 1947.

The urine was clear at all times. The lumbar puncture showed 237 cells and a Pandy test of four plus on August 29; on September 21, there were 230 cells and the Pandy test was four plus; on September 11, there were 130 cells and the Pandy test was four plus; on September 15, there were 464 cells (all mononuclears) and the Pandy test was four plus. The spinal fluid sugar went as low as 17 mg. per cent. Concentration tests for organisms in the spinal fluid were negative. Injections in the guinea pig were positive.

On x-ray examination, no evidence of pulmonary tuberculosis was found, but there were many calcific nodules in the spleen, and a diagnosis of primary tuberculous complex of the spleen was made.

## COMMENT

Two of the patients described showed good clinical response to streptomycin therapy, but the prognosis in both cases is still grave.

Case 2 showed some response but continued to have visual disturbances and signs and symptoms of hydrocephalus when he was discharged from the hospital, so that he is now blind even though the disease seems to be temporarily arrested.

Case 5 seems to have improved.

The remaining patients showed little or no response to streptomycin, and this result corresponds well to those mentioned in Feldman's series.

By determining the content of streptomycin in tissues of the various organs at necropsy, Baggenstoss and his associates[7, 8] have shown that following large doses of streptomycin (10 Gm. intramuscularly), significant amounts were found in the blood (120 μg per gram), cerebrospinal fluid (15.8 μg per gram), kidney, spleen, liver, etc. The brain, however, was completely devoid of the drug. Furthermore, pathologic evidence of healing within the miliary tubercles was evident in the lungs, liver, etc., while there was a lack of any signs of regression in the tubercles in the brain.

The fact that streptomycin reaches the cerebrospinal fluid through the blood stream and/or by intrathecal injection may explain the early clinical response occasionally observed in isolated cases. However, the tuberculous process is often initially seeded in the brain as well as in the meninges, and since the process in the meninges often extends into the brain substance, where neither streptomycin is present nor healing evident, the poor prognosis and eventual poor outcome of patients with tuberculous meningitis become apparent. Although streptomycin has given us some hope in the treatment of tuberculous meningitis, much is yet to be desired toward complete recovery from this disease.

In general, the object of treatment is to give large doses of streptomycin and thus maintain a high blood level so that the local concentrations of the drug remain high.

In adults the intramuscular administration of 1.0 Gm. of the drug at six-hour intervals is ordinarily adequate for most infections. This amounts to 4 Gm. per day. Larger doses are sometimes necessary, and up to 8 Gm. may be used if necessary. Infants and children require smaller doses—30 to 75 mg. per pound or 0.25 to 2.0 Gm. daily are adequate.

Intramuscular injection is the parenteral method of choice. In some cases intrathecal administration has been used to supplement the intramuscular route. Intrathecal doses should be smaller, and 25 mg. a day have been reported in infants without serious effect. Injections of more than 50 mg., however, may produce signs of meningeal irritation since there is a chemical irritation giving rise to arachnoiditis.

The use of streptomycin is not without danger and toxic effects. Local reactions are common and consist of pain and induration at the site of injection. This is a minor reaction and can be lessened by giving procaine simultaneously. Constitutional reactions are varied and are more severe. Headache, nausea and vomiting, and flushing of the skin have been reported. These may be due to impurities in the drug. Skin lesions vary from erythematous to hemorrhagic, urticarial to maculopapular. An interesting finding is eosinophilia with or without a skin rash.

The most important reaction is the disturbance of function of the eighth nerve, which probably represents a neurotoxic action of a selective nature. The disturbance is both vestibular and cochlear. Vertigo is prominent, and the Romberg test is positive in most patients. This disorder seems irreversible, but patients soon compensate for the defect by other postural mechanisms so that

symptoms are alleviated after a month or so. Deafness also occurs due to cochlear damage. Tinnitus generally precedes the deafness, which may be temporary or permanent. Cases have been reported in which hearing returned following cessation of therapy, only to become impaired again when streptomycin was reinstituted.

At the present time, there are six additional patients being treated for tuberculous meningitis in this hospital. One has an additional bone involvement and cold abscess and is just about holding his own. The remaining five patients are improving clinically much as in our earlier cases.

## SUMMARY

The case histories of nine patients ill with tuberculous meningitis and treated with streptomycin have been reviewed. In two, temporary clinical response was obtained.

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# THE IMPORTANCE OF PEDIATRIC AND SURGICAL CARE IN THE PREVENTION OF SELECTIVE SERVICE REJECTIONS

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A RECENT study by Dr. I. G. Greer of five large white orphanages in North Carolina (Presbyterian Orphans' Home, Methodist Children's Home, Methodist Orphanage, Oxford Masonic Orphanage, and Baptist Orphanage) showed that 1,138 men and women who grew up in these institutions were accepted by the armed services and only sixteen or 1.4 per cent were rejected.[1] The national percentage of rejection for white men who had not previously been examined was 36.1. For the same group in North Carolina as a whole the percentage was 44.6.

It is possible that the high North Carolina rejection ratio was due to the fact that the State had the highest rate of volunteers—many youths who believed that they could pass the physical examination did not wait for the draft. As a result, many of the Selective Service registrants in North Carolina were physically unfit. It also is possible that the low percentage of orphanage rejections was partially due to the fact that some orphans with irremediable defects were not accepted by the orphanages and were sent to special hospitals. However, even with this correction the conclusion is inescapable that the good pediatric care, periodic examinations, the correction of remediable defects, and the balanced diets which the orphans received were responsible for their health. The reports from the National Headquarters of the Selective Service System[2, 3] have therefore been analyzed, in order to determine the conditions and defects which could have been corrected by competent pediatric and surgical care during infancy and childhood so that the incidence of Selective Service rejections could have been reduced.

Musculoskeletal abnormalities were the leading cause of rejection in white registrants, accounting for 8 per cent, and ranked second in Negroes, representing 4.3 per cent. Deformities resulting from rickets are preventable in infants by adequate diets and early administration of cod liver oil. Such deformities as genu varum, valgum, and recurvatum can be corrected by orthopedic surgery. Abnormalities of the spine, which include scoliosis, lordosis, and kyphosis, are often corrected early in life by exercises. Arthritis, ankylosis, and atrophy may be arrested before disabling deformities can result by early definitive treatment. Torticollis and the residuals of osteomyelitis can be corrected by specific orthopedic surgery.

The incidence of hernias was found to be the second cause of rejection in whites (6.3 per cent) and third in Negroes (3.2 per cent). It is well known that some inguinal and femoral hernias in infants disappear spontaneously and may be reduced easily. Surgical treatment results in a good prognosis if the

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operation is deferred until the age of 2 years. Strapping with adhesive tape is usually sufficient for umbilical hernias in infants, although if they are very extensive an operation may be necessary.

Conditions classified as neurological included residuals of poliomyelitis, chorea, enuresis, and epilepsy. This group ranked third in whites and fifth in Negroes as cause for rejection which could have been corrected. Obviously, individuals afflicted by residuals of poliomyelitis cannot be completely rehabilitated by corrective orthopedic surgery, but many can be restored to functional activity. The incidence of poliomyelitis during epidemics can be lowered by delaying elective tonsillectomies and adenoidectomies. Certainly little can be done preventively for congenital and Huntington's chorea. In children, enuresis is often due to poor habit-training. Idiopathic epilepsy, although not preventable, can usually be controlled by proper medication.

Eye defects were the fourth most frequent cause of rejection in whites and eighth in Negroes. Errors of refraction, such as astigmatism, hyperopia, and myopia, require early expert ophthalmic care and refraction. Deformities such as ptosis of the eyelid, ectropion, entropion, dacryocystitis, pterygium, and strabismus can also be corrected by ophthalmologic surgery. Insufficient or poor lighting is responsible for many cases of asthenopia. Prompt consultation by an ophthalmologist after diagnosis will prevent more serious defects.

Conditions of the ears ranked fifth as a cause for rejection in white registrants. Otitis media and complications such as mastoiditis, brain abscesses, and lateral sinus thrombosis have become much less a problem with sulfonamide and penicillin therapy. Children with frequent upper respiratory infections and otitis media can be aided immeasurably by adenoidectomy and tonsillectomy.

Tuberculosis ranked sixth in whites and seventh in Negroes as a preventable cause for rejection. Routine tuberculin tests and x-rays of positive reactors are more valuable aids in the detection of tuberculosis than are physical examinations. The early recognition of active pulmonary tuberculosis and isolation with treatment will reduce the incidence of tuberculosis. The importance of pasteurization for the prevention of milk-borne infections is well recognized. The household use of raw milk, however, by supposedly educated parents is not uncommon.

Other lung conditions in whites ranked seventh as a preventable cause of rejection. The prevention of bronchitis, bronchiectasis, lung abscess, and empyema can be accomplished by the early use of sulfonamides and penicillin, by early and adequate treatment of dental caries, and by the avoidance of nose and throat operations while pyorrhea, stomatitis, or upper respiratory infections are present. The prophylactic use of arsphenamine when foreign bodies are removed from the bronchi may prevent spirochetal abscesses. The early treatment of sinusitis, allergy, and atelectasis, and the removal of diseased tonsils and adenoids will aid in the prevention of lung conditions.

Being underweight or overweight was the eighth cause of rejection in white registrants. Adequate diet is essential for good nutrition. The population at large should be educated in regard to adequate and well-balanced diets. This type of education is now being carried out by various government agencies and life insurance companies through the press, radio, and magazines. Children

after the age of 3 years should be taught to stand, walk, and sit properly. If every child, as early as possible, is given "setting-up" exercises and is frequently instructed in good body mechanics, growth and well-being usually will be satisfactory, and postural deformities, failure to gain weight, and lack of vigor generally will be avoided. Corrective exercises in a gymnasium may be needed for those who have a poor body-mechanics. Such a program should be carried out in the schools.

Conditions of the abdominal viscera ranked ninth in the causes of rejection of white registrants. In this group, chronic appendicitis and peptic ulcer with their complications were frequently found. Peptic ulcers, which are rare in children, usually are controlled by conservative therapy, although surgical treatment may be necessary in those cases that fail to respond. Appendectomy in children is attended with a low mortality rate if performed within twenty-four to thirty-six hours after appearance of the initial symptoms. Since the diagnosis of appendicitis in children is often difficult, all patients with signs and symptoms of acute appendicitis should receive the benefit of the doubt and be operated upon. Older children and adults with recurrent attacks of appendicitis should have their appendices removed.

Syphilis in Negroes accounted for 20.5 per cent of the preventable rejections, being the leading cause in that race. Ignorance, poverty, and indifference are the main factors responsible for this high incidence. Routine serologic tests on all parturient women and on all infants, and recognition of syphilitic stigmata should result in a decrease of congenital syphilis.

The obvious neglect of dental care is evidenced by the high incidence of teeth defects. An adequate vitamin diet, regular brushing of the teeth, and visits to the dentist are essential for healthy teeth. In addition to vitamins, the child's diet should contain at least 1 Gm. each of calcium and phosphorus daily. The deciduous teeth should be preserved in good condition as long as possible since their early loss may be responsible for faulty alignment of the permanent teeth, and caries.

Deformities of the feet ranked sixth in Negroes and tenth in whites. Most types of clubfeet respond well to orthopedic treatment if treated early. Pes planus can usually be corrected early by proper foot exercises. Callosity, corns, bunions, and hallus valgus can be prevented by instruction as to properly fitting and constructed shoes.

Skin defects were especially prominent in the white registrants. Acne vulgaris, if seen early between the ages of 8 to 12 years, during the "blackhead" stage, can be controlled in over 80 per cent of adolescents by keeping the skin dry and rather chapped, and by the use of mild and later stronger soaps and of lotio alba of increasing strength. Dietary therapy may be beneficial. Fungus conditions, especially of the feet, are controllable by keeping the feet dry and using fungicidal powder or ointment. The underlying sensitivity producing eczema at present cannot be prevented, but eczematous children should be protected against infections and extreme cold, and should not be given eggs, serum, or vaccines unless absolutely necessary and then only with extreme caution.

Furunculosis can be prevented by cleanliness of the skin and the immediate application of an antiseptic solution to abrasions. Children should be taught that abscesses should not be squeezed. High vitamin diet and injections of autogenous vaccines or staphylococcus toxoid may also be useful. Personal cleanliness is probably the best preventive measure for impetigo, scabies, or pediculosis.

Among the white registrants, nasal defects were very frequent, septal deviation and hypertrophy of the turbinates being commonly found. Unless the obstruction requires immediate attention, it should be corrected surgically in children after the age of 6 years. Nasal polyps should be removed surgically if they are producing symptoms. Sinusitis occurs more frequently in children who are allergic or who have frequent upper respiratory infections, and usually requires radical treatment to prevent bronchiectasis. If the sinusitis is due to allergy, the patient should be desensitized to the offending protein. Occasionally the reverse is true and allergic conditions are caused by chronic sinusitis; the symptoms disappear after the sinuses have been drained.

Throat conditions were among the leading causes of rejection. Of this group, tonsillitis and pharyngitis had the highest rate. Individuals who are more susceptible to tonsillitis and pharyngitis should avoid exposure to people infected with colds, since colds precede more severe infections of the rhinopharynx. If children who have "just a slight cold" were urged to stay home from school and were kept in bed at the onset of illness, recovery would be more rapid and contact cases avoided. Susceptibility to colds would be reduced if the humidity in the home and classroom were increased. Approximately 20 per cent of children after the age of 3 or 4 years should have their tonsils and adenoids removed, especially those who have had repeated respiratory infections with persistent cervical adenopathy, markedly enlarged tonsils with obstructive symptoms, chronic otitis media, rheumatic fever, acute glomerulonephritis (following tonsillitis), and childhood tuberculosis, and those who are diphtheria carriers; at least 50 per cent of this group are benefited. Removal of adenoids is indicated in infants who have nasal obstructions, chronic otitis media, or sinusitis.

Varicoceles, hydroceles, and hematoceles are rare in children. If present in infants, hydrocele usually disappears before the age of 2 years without treatment. Scrotal suspensories, aspiration, or injection may be advisable. Occasionally surgical treatment is required. For the prevention of balanitis, paraphimosis, and phimosis, cleanliness of the penis is essential, and circumcision should be done if the foreskin is redundant or difficult to retract. Chordee should be repaired surgically at the age of 3 years, and plastic surgery for hypospadias and epispadia should be done at 6 to 8 years of age.

Gonorrhea and other venereal diseases were prevalent in Negroes, being the eighth leading cause of rejection. Prevention in adults can be accomplished in great part by proper sex instruction of children, preferably in the home, and by educational measures as carried out in the armed forces.

Last but not least, it is likely that the quiet, regimented life which the orphans had led, in spite or because of its obvious lack of parenteral attention, was an important factor in their low percentage of rejections because 12 per cent of all Selective Service rejections were due to neuropsychiatric disorders.[4]

## CONCLUSION

At risk of carefully delineating the obvious, to quote William James, better pediatric and surgical care might have decreased the incidence of Selective Service rejections. An analysis of the reports of Selective Service shows that many of the causes of rejections might have been prevented or corrected during infancy and childhood. Lack of pediatric care is mainly due to ignorance on the part of parents who rarely think in terms of prevention but call for medical aid only when the child is ill.

The purpose of this paper is to emphasize the need for better pediatric care, and to discover why the Selective Service rejection rate of the graduates of the North Carolina orphanages was so much lower (1.4 per cent) than that for the State (44.6 per cent).

## Addendum

Dr. Maurice H. Friedman, speaking at the third annual meeting of the National Conference on Rural Health held in Chicago in February, 1948, reported the following conclusions:

1. There was no significant difference in the per cent of rural and urban youth selected for the armed service. Actually the data show more rural white men were accepted for service than urban white men.

2. The percentage of Negroes accepted for service was far less. Over two-thirds of Negro rejections were accounted for by syphilis, educational and mental deficiency, and mental disease.

3. Detailed examination of all recorded defects in Illinois, Indiana, and Iowa shows no significant differences between the rural and urban populations, even though the cream of the farm youth was kept on the farms by priorities and never appeared for examination.

4. This does not entitle us to conclude that the health of the farm youth is as good as the health of the urban youth. On the basis of the Selective Service statistics we cannot draw any inferences as to the health of the farm youth since these statistics are not a reliable guide to the health of a community.

5. Conclusions regarding the medical care of a community cannot be drawn even when the "health" of a community is reliably and accurately measured, for medical care is only one of many factors which determine community health.

6. With respect to many diseases, socioeconomic factors, such as geography, density of population, housing, race, and ethnic or cultural background, are of more importance than the availability of medical care.

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# Case Reports

## PRECOCIOUS PUBERTY WITHOUT A DEMONSTRABLE TUMOR

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PRECOCIOUS puberty was once thought to be due entirely to a disturbance of one of the endocrine glands and most often to a tumor of one of these glands. Cases have been recorded of sexual precocity caused by granulosa cell tumor of the ovary,[1] adrenal tumor or hyperfunction,[2] testicular tumors, central nervous system lesions, especially midbrain neoplasms, and more rarely tumors of the pituitary and pineal glands.[3]

Novak has reported a group of cases of a type of precocious puberty which he says is the most common of all, the constitutional type. The etiology is unknown, but it is postulated to be due to an abnormal genetic factor. It is his opinion that children with constitutional precocity develop a perfectly normal puberal phenomenon at an abnormally early age, skipping the childhood period between infancy and adolescence.

The clinical picture of female children of this group is that of a child who is larger than her chronological age, has varying degrees of development of the secondary sexual characteristics, and has an adult type of reproductive organs with a regular menstrual period. Even ovulation occurs in this group.[4]

It was felt that the following case most probably fits in this category.

### CASE REPORT

A. L. K., a 3-year-old Negro girl, was admitted to the Jefferson-Hillman Hospitals on Feb. 6, 1946. The child's mother stated the child's breasts had been abnormally large at birth and had continued to grow slowly, and by the time she was 9 months old they were definitely enlarged. There had never been a discharge from the nipples. Shortly before her first birthday she began to pass some dark brown material per vagina. The material was described as being about the same color and consistency as floor wax. From this time on she began to have such periods regularly every twenty-eight to thirty days. This type of period continued for about one year, and then the character of the flow changed to what the mother described as, "Looks like what I pass during my period." The periods lasted three days, the amount of flow being approximately the same each day. During the periods the mother would put a diaper on the child, and by evening the diaper would be well soiled. On admission the child was having a period, and her panties had eighteen to twenty drops of blood on them, covering most of the bottom of the underwear.

She was the first child, being delivered in this hospital without difficulty. There were no complications in the early postnatal period. She had had none of the childhood diseases and no serious illnesses or operations.

The developmental history was normal.

So far as the mother knew the child was not aware of her condition and exhibited no libido.

*Physical Examination.*—The blood pressure was 92/54, temperature 99° F., respirations 22, pulse 84.

The child was 43 inches tall and weighed 45 pounds. The general physical development appeared to be that of a child about two to two and a half years older than the patient's stated age. The general body contour was that of post-puberty.

No abnormalities of the head or skull were noted. The eyes and eye grounds were normal. There was slightly more hair on the face than is usual for the age. She had a full complement of deciduous teeth. Nothing of note was found in the examination of the ears, nose, and throat or of the neck.

The breasts were fully developed. There seemed to be slightly less ductal tissue than in an adult breast of the same size. No nipple secretion was noted.

The lungs and heart were not remarkable. The abdomen was flat. No organs or masses were palpated. A large umbilical hernia was present.

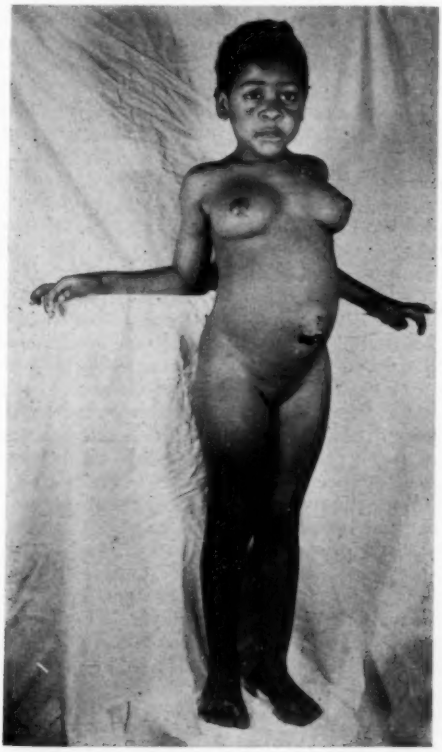

Fig. 1.—Three-year-old Negro girl showing sexual precocity. Note absence of pubic hair.

In examining the genitalia, a very slight amount of pubic hair was found. The labia majora and minora were well developed. The introitus easily admitted one finger. Vaginal rugae, typical of those of an adult, were seen. The clitoris was not enlarged. The uterus was enlarged to the size of that of an adult and occupied a posterior position. The right ovary could be felt and measured about 2 by 3 cm.

The extremities were not remarkable, except that the fat distribution and shape were those of adolescence.

*Laboratory Data.*—The blood picture was within normal limits. Urine Kahn and Mantoux tests were negative. In a twenty-four hour urine sample, 1.5 mg. of ketosteroids and less than 6.6 mouse units of gonadotropic hormone were excreted. These amounts are within normal limits for the age.[5]

Anteroposterior and lateral views of the skull showed no abnormalities. The bone age was found to be that of an 8-year-old. The long bones appeared normal.

The patient had an I.Q. of 85 to 100 and a mental age of 3½ to 4 years.

About ten days after the last menstrual period, a cervical and vaginal smear was made and stained. It was found to contain stratified squamous epithelium, similar to that found in adults showing estrogenic activity.

Twenty-five days after the beginning of the last menstrual period, under general anesthesia, a pelvic examination was done. Findings were essentially the same as on admission. At this time a dilatation and curettage were done. The pathologic report was: "Two to three cubic centimeters of soft, grayish brown endometrial scraping submitted. The endometrium is composed of numerous glands, which are fairly large and dilated in some areas. The epithelium is tall with basally placed nuclei. There are no secretory vacuoles present. The stroma is dense. Impression is that the endometrium is in a proliferative phase."

Since it is known that a very small tumor of the ovary can produce such a picture, and due to the fact that the uterine scrapings did not show ovulation, it was felt that a laparotomy was justified to search for an ovarian tumor.

On March 12, 1946, under ether anesthesia, a low midline incision was made and the pelvis explored. The right ovary was partially resected, removing an old retention cyst. The left ovary was normal except for a few small cysts, which were punctured with a needle. An appendectomy was done and the abdomen closed. The pelvic organs were said to be the size of those of a 15-year-old girl.

The pathologic report on the ovarian tissue was: "The specimen is a portion of an ovary which consists of essentially a thin-walled cyst covered with white tissue. The lumen is empty, and the wall is red. A question of lutein was present at operation; however, nothing suggesting lutein tissue is present in the gross specimen. On microscopic examination, the ovary contains many primordial follicles and one ripening Graafian follicle. There is a small proliferous cyst. Nowhere in the section is there anything suggesting lutein tissue."

The patient made an uneventful recovery. After explaining her condition to the mother, the patient was discharged to the outpatient clinic.

Since then she has been seen twice. She has gained 2 pounds, and her menstrual periods have increased to four days. The amount of flow has also increased. Other attempts to admit the child for endometrial scrapings to look for definite evidence of ovulation have failed since she would not re-enter the hospital.

## SUMMARY

A case of precocious puberty has been presented. It is felt that this case probably should be classified as the constitutional type of Novak, although definite proof of ovulation was not obtained.

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# URETHRAL BLEEDING IN MEASLES

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A 7-YEAR-OLD girl in the third day of the eruptive stage of rubeola began to bleed from the vulva. The mother applied sanitary pads, three of which had become saturated with blood before the child was examined by a physician. Inspection revealed a large, firm blood clot distending the urethral meatus. Some blood was seen oozing around the clot, and she was able to void around it. The clot was grasped with a forceps and part of it broke off; the remaining portion seemed to be adherent to the urethral wall above. It was not disturbed further, and there was no more bleeding. The appearance of the lesion suggested a bleeding polyp or some type of urethral tumor, which would be a rare lesion in a child this age. One of the country's outstanding urologists happened to pay me a visit at this time, and because the case was unusual he kindly consented to see the patient with me. He, too, thought she probably had a pre-existing lesion in the urethra, and we decided that she should be examined after she recovered from the measles, and if a polyp or tumor was present, it should be treated accordingly. The child was examined two weeks later, and the area was entirely healed. The attack of measles seemed to be very ordinary in other respects and there was no other bleeding.

I have been unable to find a reference regarding bleeding from the urethra in measles, though hemorrhage from the mucous membranes, mouth, nose, and intestinal tract is known to occur.[1] In conversing with pediatricians, I have been unable to find one whose experience has included a patient with such a complication.

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From the Department of Urology, University of Georgia School of Medicine, Augusta.

# HYPERTROPHIC PYLORIC STENOSIS IN A NEWBORN INFANT

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THIS is a case report of hypertrophic pyloric stenosis in a newborn infant. Symptoms of obstruction of increasing severity developed on the second day of life. The infant was successfully relieved by the Fredet-Rammstedt operation on the fourth day of life. After a difficult postoperative period, growth and development continued in the usual fashion.

## CASE REPORT

*History.*—C. D., a white infant girl, weighing 8 pounds, 3 ounces, was delivered at term of a mother 41 years of age, para iii, on Dec. 12, 1947, after a four-hour labor. Spontaneous cry and respirations were vigorous. The father, 46 years old, and three other children, a son 24 years, a daughter 11 years, and a son 5 years of age, were living and well. The daughter was a feeding problem from birth. It was necessary to give her drops of atropine before each feeding for the first six weeks of life to prevent vomiting.

*Clinical Examination.*—The infant was seen the morning of Dec. 13, 1947, by the pediatrician on duty, and appeared normal on physical examination. There was no evidence of intracranial injury.

At 12 hours of age, 5 per cent glucose water was offered by mouth every four hours. At 24 hours, ward evaporated milk formula was offered every four hours. On Dec. 14, thirty-six hours after birth, the first afternoon feeding was forcefully ejected through the nose and mouth in projectile fashion fifteen minutes after the end of the nursing period. The infant was again placed on 5 per cent glucose water feedings. These were partially returned with retching, along with thick, viscid mucus. No bile staining occurred. The infant was passing small quantities of urine and meconial stool at four- to six-hour intervals. The left upper quadrant was moderately distended. There was audible borborygmus in the small intestine, and the infant passed flatus during the examination. Digital examination of the rectum was normal. Atropine sulfate solution (1:1,000), increasing from one to three drops, was administered before feedings. Formula was thickened with cereal. Twenty cubic centimeters of isotonic saline were given subcutaneously every three hours.

The child improved and all feedings were partially retained for two days, and then forceful, complete return of feedings began fifteen minutes after they were taken. The weight at this time was 7 pounds, 9 ounces. The evening nurse had reported a small quantity of milk stool in the last meconial bowel movement. Mild icterus neonatorum had developed. There was a high-pitched, agonized cry of pain at frequent intervals. The eyelids were quite edematous. Inspiratory râles could be heard at the right base posteriorly and in the left axilla. The cord had dropped off, leaving a slightly infected, moist stump. The liver was 4 cm. below the costal margin in the midclavicular line. There was marked distention of the left upper quadrant. No waves could be made out. Attempts to palpate a pyloric tumor during nursing and after vomiting were unsuccessful.

Laboratory data: hemoglobin 14.0 Gm., red blood cell count 5.17 million, white blood cell count 14,400 with 53 per cent polymorphonuclears, 36 per cent lymphocytes, 8 per cent myelocytes, 3 per cent eosinophiles. There was no growth in the blood or in catheterized urine cultures. The urinalysis was normal.

The infant was given 20 c.c. of Lipiodol by nipple, and fluoroscoped. The oil encountered difficulty passing the cardiac sphincter but did go through finally

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in small squirts. By change of position and abdominal massage, a small drop of oil was milked through a string-sized pyloric canal and moved rapidly into the jejunum. There was a lemon-shaped shadow on the film with a nipple protrusion into the pylorus. The three-hour film demonstrated considerable retention with a little oil in the small intestinal loops (Fig. 1).

*Diagnosis.*—A diagnosis of pyloric obstruction with stenosis was made, and an exploratory laparotomy was advised.

Fig. 1.—Roentgenogram taken preoperatively showing retention of Lipiodol in stomach and nipple-like projection at pylorus.

*Operative Note.*—The infant was taken to the operating room in good condition, and an infusion of 5 per cent glucose in saline was started. Open drop ether anesthesia was administered. A high, vertical, right rectus-splitting incision was made. There was no free fluid in the abdomen. The stomach was moderately dilated, and the pylorus contained a definite lemon yellow tumor approximately 2.0 cm. long, of almost cartilaginous consistency. No other abnormalities were found. The serosa was opened by sharp dissection over the entire length of the tumor, and the underlying muscle was separated to the mucosa. There was slight oozing but no free bleeding. At the completion of the Fredet-Rammstedt procedure, the pyloric mucosa was seen to pout up into the muscular defect, affording relief of the previous obstruction.

*Postoperative Clinical Course.*—The infant was returned to the ward in good condition with a Wangensteen suction in place and the remainder of 100 c.c. of whole citrated blood run in by slow drip. Suction was discontinued the next day and 5 to 10 c.c. feedings of 5 per cent glucose water were offered by dropper every two hours. During the next two days the infant partially

or completely regurgitated feedings by mouth, usually quite promptly after being fed. On December 19, two days later, the infant was again fluoroscoped and offered 20 c.c. of Lipiodol by nipple. There was marked cardiospasm and some dilatation of the esophagus. This spasm was dilated with a gavage tube. Oil promptly passed on through into the intestinal tract (Fig. 2). Peristalsis and reverse peristalsis from the jejunum on up were extremely active.

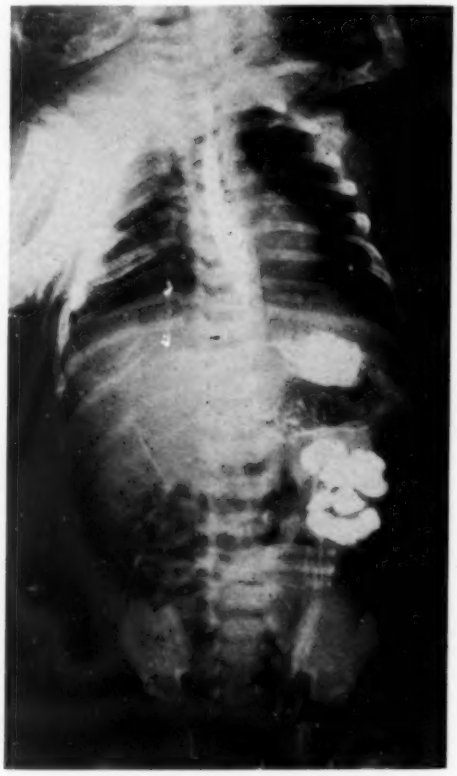

Fig. 2.—Postoperative x-ray revealing prompt passage of Lipiodol into small intestine but partial retention in esophagus.

During the next four days, hydration, and urinary output were maintained as indicated with 100 c.c. hypodermoclyses of 5 per cent glucose in distilled water or isotonic saline. The infant was given sodium luminal gr. ¼ every six hours by hypodermic injection, and atropine by mouth or by injection to the point of intoxication before each feeding. The nursing staff fed the infant cereal-thickened formula by Breck feeder or gavage. Repeated regurgitation of bile-stained stomach contents continued unabated.

The wound healed clean and well. On December 23, the first normal-sized, soft yellow bowel movement appeared. Thereafter, regular movements continued which were normal in size and consistency. Clyses were discontinued.

The infant developed a temperature of 101° F. by rectum on December 27. Examination revealed a purulent nasal discharge and a slightly infected pharynx. The nose and throat culture grew out *Staphylococcus aureus* and

*Escherichia coli* bacteria. Therapy consisted of 10,000 units of penicillin every three hours for three days, by hypodermic injection. Recovery from the respiratory infection was complete.

Atropine and thickened feedings were discontinued on December 30, and the child was placed on an evaporated milk and Karo formula. She was discharged on Jan. 2, 1948, the seventeenth postoperative day, weighing 8 pounds, 7 ounces. The hemoglobin was 16 Gm., the red blood cell count 5.5 million, the white cell count 9,500 with a normal differential. Urinalysis was normal.

The patient was seen in the outpatient clinic Jan. 7, 1948, at which time she weighed 8 pounds, 11 ounces. On February 10, at 9 weeks of age, she weighed 11 pounds, 2 ounces, and the length was 23 inches. There had been no vomiting. The child's development was normal.

## DISCUSSION

MacHaffie[1] reported a similar case of an infant girl with hypertrophic pylorie stenosis who was operated on at 34 hours of age. No other report of this condition producing obstruction in the newborn period has been found in the literature. Our patient was operated upon with the thought in mind of relieving a pyloric obstruction due to congenital stenosis, as a pyloric tumor seemed only an academic possibility.

The etiology of hypertrophic pylorie stenosis is not clear. The question arises whether the hypertrophy of the circular smooth muscle sphincter with stenosis precedes or follows pylorospasm. Wallgren,[2] in careful serial x-ray studies, concluded it was improper to speak of this condition as "congenital." Donovan[3] and Ladd and Gross[4] mention finding the tumor in premature infants and in other infants too early in life for spasm to have caused the hypertrophy. Donovan states there is no correlation between the size of the tumor and the age at operation, and makes the point that the variation in the severity and the time of onset of the symptoms seems to be due to the amount of pylorospasm rather than the size of the tumor.

In our patient, the tumor was congenital. The spasm developed on the second day of life. It was not amenable to medical care. Obstruction was confirmed by x-ray examination. The postoperative course was jeopardized by severe cardiospasm, undoubtedly aggravated by suction and gavage tubes. It is of interest to note that MacHaffie's patient and our own were female infants, the third and fourth pregnancies, respectively, and both showed only a distention of the left upper quadrant, without a wave or tumor demonstrable. The postoperative course in both cases was complicated by continued vomiting for several days. Our patient's sister had a milder but possibly similar condition, relieved by atropine.

## SUMMARY

A case of hypertrophic pyloric stenosis with obstruction is reported, which developed on the second day of life and was successfully relieved by operation on the fourth day of life. Attention is called to the report of another case. The infant was female, the fourth child of middle-aged parents, and had a fully developed pyloric tumor with cardiospasm and pylorospasm of marked degree. The infant was discharged on the seventeenth postoperative day, above birth weight, and her subsequent growth and development have been normal in all respects.

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# Medical Care

## THE MANAGEMENT OF INFANTILE ECZEMA FROM THE PEDIATRIC-DERMATOLOGIC POINT OF VIEW

### A Therapeutic Consideration Based Upon the Pathogenesis of the Dermatoses

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THE etiology of eczema in infants and children continues to be shrouded in obscurity. With the exception of those few instances in which food allergens and inhalants play important etiological roles and in which their elimination solves the problem, the management of eczema is little different from what it formerly was. In brief, the therapeusis of infantile eczema comprises chiefly the use of certain topical remedies prescribed in answer to the facts observed by the pathologist and clinician and conformable to well-established practices developing from those data. In spite of therapeutic advance, no specific remedy for this dermatosis has yet been discovered.

#### WHAT IS ECZEMA?

The term eczema has been loosely employed to cover a multitude of dermatologic entities. Infantile eczema is also used as a synonym for atopic dermatitis in infants. "Atopic" denotes a type of allergic hypersensitivity appearing in human beings but not in lower animals, and characterized by a strong hereditary disposition as shown in the eczema-asthma-hay fever complex. Individuals with atopic dermatitis will have a familial history of allergy; antibodies can be demonstrated in their serum by the Prausnitz-Küstner passive transfer test; eosinophilia is frequently present; and they usually respond positively to scratch or intracutaneous tests by an urticarial wheal and flare. In older children and adults true atopic dermatitis is known by a variety of other names: lichen simplex chronicus (Vidal) or neurodermatitis disseminata, the late "exudative eczematoid" of Rost, the prurigo diathesique of Brocq, and the prurigo of Besnier.

Eczema venenatum or dermatitis venenata is a contact dermatitis and is caused by many extrinsic factors including contact with chemicals, plants, and topical medications. Eczema intertriginosum (intertriginous eczema, eczema intertrigo) is characterized by hyperemia. This condition is known as chafing and is frequently seen in the groin and axillae and beneath the breasts in women. Finally we might mention "mycotic" or "nummular" eczema.

To the dermatologist, atopic dermatitis is a definite entity comprising certain well-defined changes in the histopathologic pattern of the skin. The exact description of this pathogenesis is the best definition of the dermatosis.

## PATHOGENESIS OF ATOPIC DERMATITIS

Although from a practical point of view there exist no sharp lines demarcating the various phases of eczema one from another, it is perhaps best to discuss the various manifestations seriatim in order to understand clearly the pathologic changes that take place in the corium and in the epidermis.

All eczemas begin as an erythema. The shock organ in atopic eczema is located in the superficial blood vessels (the smaller capillaries and the arterioles) in the upper cutis. It is at that point in the dermatologic network that the allergen (irritant) exerts its damaging influence and so sets in motion a cycle of changes which follow each other in ordered sequence. Histologically these changes occur for the most part in the epidermis, but the corium shares in them, too. There are several ways in which the highly sensitized skin reacts to the allergenic agent. But first, for understanding them, it must be realized that in atopic eczema the skin is different from normal integument in that it is predisposed from the time of the infant's birth to react in a peculiar manner. A large percentage of the parents of eczematous infants, upon being questioned as to the existence of an allergy either among the members of the immediate family or among closely related persons, admit the existence of the condition denominated by Stokes as "the asthma-hay fever-angioneurotic complex." In some studies a positive family history of allergy in as high as 40 to 60 per cent of cases has been obtained. Some children may become sensitized by allergens during their intrauterine life or during nursing. Ratner and others have demonstrated that such sensitization actually does take place through the placenta and through breast milk. Once an infant has become so sensitized, he will always react to the presence of the particular allergen by a regular train of symptoms and signs whenever he comes into contact with it.

The clinical picture of eczema is well known to all pediatricians. After the initial stage of erythema, there follow, as stages in the dermatosis, edema, vesiculation, exudation, and crusting. In favorable cases, healing of the lesions is preceded by scale formation. Various stages of the eczematous condition are often present together. Relapses are frequently seen even when improvement has progressed to the healing stage; even then late edema and oozing may recur. In spite of these irregularities, a diagrammatic representation of the progressive stages of eczema has its use (see Fig. 1).

The histologic picture of eczema in older children and adults is similar to that in infants, except that in very young infants the stratum corneum is thin so that there is lacking the resistance to the edematous fluid furnished by the strongly functioning corneal layer of the older person, with the result that vesiculation and bullous lesions occur much more frequently.

Soon after the allergenic agent has exerted its harmful effect upon the superficial blood vessels of the upper corium, the capillaries enlarge and fill with blood (erythema). The simple inflammatory exudate that surrounds these vessels (defense mechanism) consists of small round cells (small lymphocytes) and wandering connective tissue cells (histiocytes). After the primary insult to the vessels, an outpouring of serum takes place sufficient to invade the

epidermis. Clinically this constitutes the stage of edema. Histologically the edema is of the interstitial type—that is, the prickle cells are not themselves particularly "water-logged" but the interstices of the cells, especially the spaces between the prickle cells, those little "bridges" connecting one prickle cell with another, become the chief site of the edematous change. Varying degrees of edema, dependent upon the mildness or severity of the eczema, can be seen. Thus, in comparatively mild cases the contour of the epidermis is fairly well retained, and its staining property is only slightly affected. On the other hand, in moderately severe or severe cases of eczema, the prickle cells and their staining property are altered (light staining). This alteration, called spongiosis, may lead to the rupture of the prickles. When, in turn, these ruptures become confluent, the result is a vesicle or a series of vesicles. Increased serum to the epidermis means increased nourishment, and the result is the hypertrophy of the prickle cell layer, an acanthosis. Happily the pathologic process in eczema is reversible, so that under conditions of adequate therapy the edema may be made to subside, with restoration of the normal skin following in course. To avoid deep scratching and infection I restrict the motion of the hands by splints and other similar devices.

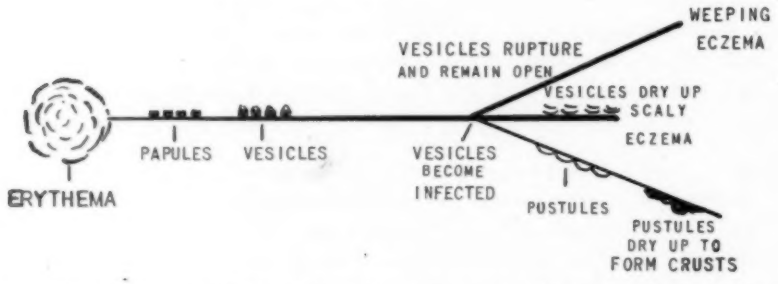


Fig. 1.—Schematic representation of the stages of eczema. (After MacKenna, R. M. B., Diseases of the Skin, ed. 4, London, 1937, Bailliere, Tindall & Cox.)

## CLASSIFICATION

There are many classifications of eczema in infants and children, several of which are confusing. Perhaps the classification of Sulzberger is best from a combined pediatric and dermatologic practical viewpoint. Sulzberger[1] points out that "Proper classification is important since it determines the therapeutic approach, the prognosis and the proper prophylactic measures."

I have proposed the following classification of eczema in infants and children, which seems of practical usefulness inasmuch as it indicates the distribution of the lesions under the atopic type.

### *Atopic Dermatitis* (Infants Under 2 Years)*

1. The usual areas: Mostly the antecubital and popliteal regions, both sides of the face, and forehead. A single area may be involved or all three regions

*This type of eczema may be preceded by the seborrheic variety.

may be affected at the same time. This disseminated variety is similar to the lichen chronicus simplex circumscriptus of Vidal (circumscribed neurodermatitis) in the classification given by Sulzberger. (See Fig. 2.)

2. The inverse type: The lesions occur upon the extensor surfaces of the elbows and the adjoining surfaces of the skin. The extensors of the thighs and legs are similarly affected. The face may share in the process. (See Fig. 3.)

3. The combined types: Any part of the body may be involved: i.e., the antecubital and popliteal areas with indurated, and lichenified plaques upon the face, chest, buttocks, and elsewhere. This variety of eczema is synonymous with the lichen chronicus disseminatus of Vidal and is the type designated as atopic dermatitis by Coca and Sulzberger. (See Fig. 3.)

Fig. 2.—The usual type of atopic dermatitis male infant aged 7 months. Note the sharply demarcated and infiltrated plaques upon both cheeks, which consist of erythema, papules and papulovesicles. Many of the latter lesions have been denuded due to scratching. A number of discrete papules and scratch marks are also seen upon the chin. Similar lesions were demonstrable upon the antecubital and popliteal areas. The patient represents the so-called "wet stage"; considerable "oozing" of the lesions was present at this time. A positive history of bronchial asthma was elicited in the father. The mother has hay fever. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, New York.)

## THERAPEUTIC INDICATIONS

1. *Rest.*—Physiologic rest is always important for the welfare of infants, but it is even more important for the infant victims of eczema because of their greater losses of energy owing to restlessness, constant crying, and refusal of nourishment. It may be achieved by several means—mechanical, by splinting and other devices, and medicinal, both topical and internal.

Among topical remedies, the colloidal bath in the form of starch, oatmeal, or bran bath is valuable since it serves to allay acute erythema and itching. Accordingly, because of gratifying results, I have made it a rule to instruct mothers in the routine of the starch bath in all cases of eczema. For a proper preparation, the corn starch (Argo or Linit, which are already hydrolized, will serve)

should be mixed with water and stirred with a spoon or a wooden stick until the mixture is milky white, and then added to the bathtub of water. Ordinary starch should be prepared as just described and then transferred to a pot over low heat and stirred until it assumes the appearance of ground glass. Then after the paste has cooled, a portion of it is to be applied gently to the infant's skin while the remainder is to be added to a tub of water in which the infant is to be immersed. There the child may remain for five minutes, provided that the room is sufficiently warm. Then the skin may be gently wiped and patted and dried with a soft towel, but under no circumstances must it be rubbed. Such a bath may be employed every day or every second day in cool weather, several times a day in warm weather. To finish off, a fine talc (unscented) may be used to dust the skin. Talcum powder containing zinc stearate should be avoided.

Fig. 3.—Atopic dermatitis. The so-called "combined type." The patient is a boy aged 5½ years and shows in addition to lichenification, induration, denuded papules and crusts upon the usual areas (face, neck, antecubital and popliteal regions), similar lesions upon the extensors of the upper and lower extremities, representing the "inverse type" of atopic dermatitis. Duration one year. (Atopic dermatitis may involve any part of the body.) A positive history of allergy was obtained in the father. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, New York.)

A kaolin bath is soothing to a highly inflamed skin. Kaolin (*Kaolinum*, N.F.) is a native hydrated aluminum silicate, powdered and freed from gritty particles by elutriation. It is closely related to bentonite and is employed in pharmacy as a distributing and filtering medium. When added to warm water in the proportion of ¼ pound to the bathinette of water (¼ pound to 10 gallons of water) it serves as a useful soothing remedy.

Sedatives are certainly indicated at any stage, and the oral barbiturates are the best. I seldom prescribe less than 0.016 Gm. (gr. ¼) of phenobarbital sodium (soluble phenobarbital) for very young infants and frequently as much as 0.03 Gm. (Gr. ½) for somewhat older infants, to be given every three or four hours to produce *rest*. I have never seen untoward effects from the use of barbiturates when given in the manner described. On the other hand, the opiates should never be employed because by the use of them the pruritus is increased and because they are habit forming.

2. *Removal of the Offending Allergen.*—Although removal of the offending allergen remains the ideal method of achieving the therapeutic result, experience has convinced most pediatricians that for the vast majority of patients that method of approach is a waste of time, money, and effort. The scratch test is inconstant in its result. In fact, trial of foodstuffs suspected as offenders has been more successful than the skin test. I believe that more can be learned concerning the allergen from a careful history than from an occasional positive scratch test. After one year of age foods come to play a minor, certainly a less significant, role in atopic dermatitis. Regarding food allergens, Sulzberger[1] states: "The approach through the history, the close observations of the effects of elimination and re-exposure to certain foods, and the constant awareness that a certain few foods are notorious offenders will prove to be more successful, as a rule, than reliance on the results of hundreds of cutaneous tests. For although results of cutaneous tests are, in infantile eczema, often without clinical significance, even accompanied by specific reagins, conversely, substances that fail to elicit cutaneous reactions may nevertheless sometimes be factors in the production of the eruption."

When food proteins, such as cow's milk, egg, and wheat, have been found definitely to be responsible for atopic dermatitis, then, of course, these should be eliminated and replaced in the diet by equally important but nonallergenic foods. Fortunately, there is a large number of such substitutional foods upon the market, among them goat's milk, whole and evaporated, evaporated cow's milk, Mull-Soy, Sobee, and hypoallergic milks.

3. *Maintenance of Adequate Nutrition.*—The discussion of diet suggests the necessity of at least a reference to the safeguarding of the patient's nutrition. I am convinced that it is unwise to treat an infant suffering from an eczema in such a way as to endanger by a strict curtailment of foods his general health to the point of an impending acidosis and possible loss of weight. No treatment, no matter how effective from the dermatologic therapeutic point of view, is justified if the health and nutrition of the patient are actually endangered by it.

4. *The Use and Abuse of Therapeutic Topical Remedies.*—One of the reasons why the pediatrician fails to obtain improvement in the atopic eczematous infant or child is that remedial agents are too often prescribed without a clear-cut indication for their use and without regard to the stage of the eczema. The key to success in the management of dermatoses in infancy or childhood, whether they be eczemas or not, is comprehended in the formula: *Conservatism and*

*simplicity in topical remedies employed.* A considerable part of the dermatologist's practice consists in treating patients whose skin has been traumatized by the injudicious use of local remedies often prescribed by the general practitioner. This unhappy state of affairs can be attributed to a large extent to the many proprietary preparations high-pressured to the physician. Analyzing the composition of many of these proprietary ointments and lotions advertised for use in eczema, one is amazed at the strength of ingredients dangerous when applied to adults and even more so, of course, to infants and children. Good dermatology like all good therapeutics is an art. The skilled dermatologist is one who has not only a sound knowledge of the composition of the remedies he prescribes but of their correct use, including (of equal importance) the knowledge when not to use them at all. The mere ordering of a useful remedy indicated in the course of an atopic dermatitis is not sufficient; further specific instructions must be given the parent as to how to apply the agent and especially the proper application of bandages.

5. *The Use of Soap and Water.*—I am not convinced that soap and water are irritants to a normal skin although I am convinced that they are bad detergents for a "sick" skin; and for this reason I feel together with most dermatologists that the use of ordinary soap and water are definitely contraindicated as cleansing agents in atopic dermatitis. The free alkali frequently sets up a dermatitis that is especially noticeable in the diaper area. Of course, cleansing the skin is important. The constant application of greasy ointments to the lesions causes the body to give forth a disagreeable odor and also serves to irritate the skin still further. When the ordinary starch bath fails to remove the ointments and other debris (as it seldom does), then one of the newer soaps, the so-called "sulfonated" soaps, may be used to advantage. Sulfonated castor oil (N.F.) may also be used. Bland, nonirritating oils, such as warm olive oil and sweet almond oil, are excellent lubricants. However, several oils popular with mothers, containing hydroxyquinoline, are skin-sensitizers and as such are best left alone.

6. *Restriction of Motion.*—The use of handcuffs, elbow splints, and other devices to prevent scratching seems to be good therapy, contrary to the opposing opinion of some dermatologists, a considerable number of pediatricians, and sometimes mothers. It should be remembered that in atopic eczema the skin is already the seat of a dermatitis—i.e., it is acutely inflamed. Accordingly, in my opinion nothing could be more absurd than to permit an eczematous baby to scratch because of itching. To do so, means to let him inflict wounds upon the already damaged skin. Furthermore the constant presence upon the skin of streptococci and staphylococci may result upon scratching in a pyoderma often rebellious to therapy. Certainly such a complication is to be avoided. I am not convinced that restriction of motion in infants will necessarily produce ties.[2] I know, to the contrary, that I have been splinting infants for over a quarter of a century without in a single instance finding the practice harmful in any way. Cutting the nails short does not prevent injury, for rubbing the skin with the hand and so traumatizing it is equally bad. Accordingly, I unequivocally endorse the use of splints.

7. *Environmental Change.*—The management of the eczematous infant or child is by no means a simple or easy task. There is a certain percentage of infants who disappointingly fail to respond to the best management. In desperation the parents have gone on to consult perhaps a half dozen dermatologists without securing improvement for their child. In these recalcitrant eczemas when orthodox therapy has been given a fair trial and failed, the effect of another environment should be tried. An extended stay at the seashore with indulgence in ocean bathing and basking in the sun will frequently produce remarkable improvement. During cold seasons when the seashore in northern climates becomes impossible, the same plan may be carried out upon a warmer coast. Although I am not enthusiastic about transferring an eczematous infant to a hospital, very often the mere change from home to the new atmosphere of the hospital will be sufficient to produce improvement.

## MANAGEMENT

The aim in management of atopic dermatitis is to restore to an equilibrium the physiobiologic mechanism of the body. In general, there are two different methods of handling the atopic eczematous infant or child although, of course, both aim at the same object—namely, the restoration of a "sick" skin to a state of health. The first of these, the pediatric approach, tends to emphasize dietetic factors of causation and to minimize the usefulness of the management of the dermatosis. On the other hand, the second approach, the dermatologic, tends naturally in terms of its practitioners' training, to direct its attention mostly to topical remedies and to ignore the etiological role of food allergens in the disturbances of some infants. (Certainly the role of the allergens is not as important as was formerly believed.) Each of these methods has its place, but the best care for the infant suffering from atopic dermatitis calls for the application of both in combination, with the pediatrician and the dermatologist both making their contributions from their respective specialties. Improvement and ultimate cure depend, in the end, not upon the utility of any single measure or device but upon the joint effort of both specialties. In the meantime any agent that can help to give the patient comfort and rest from itching and prevent recurrence is worth while, be it physical, mechanical, chemical, or galenic, whether a topical remedy, bath, sedation, or the elimination of a food allergen. (See Table I.)

*The First Stage.*—Examination of the corium and the epidermis under the microscope (see Figs. 4, 5, and 6) shows the tissue laden with fluid. This edema characterizes the process in the "wet stage"; it is a true "water-logging" of the cells of the epidermis and corium. Close examination shows that the edema is not only within individual cells (parenchymatous) but is between cells, in the interstices of the epidermis (interstitial). Edematous tissue stains badly (hematoxylin-eosin), appearing much lighter than normal tissue. The capillaries are dilated, and their endothelial cells are swollen.

At this stage the most important therapeutic indication is the ridding of the water-logged tissues of their fluid content. This draining away of fluid can

TABLE I. SYNOPSIS OF MANAGEMENT OF ATOPIC DERMATITIS

| | FIRST STAGE (ACUTE) | SECOND STAGE (SUBACUTE) | THIRD STAGE (CHRONIC) |
|---|---|---|---|
| Pathologic picture of the skin (Simplified) | Edema (spongiosis to vesicles in epidermis). Dilated blood vessels and edema in upper cutis. Inflammatory infiltration in upper cutis | Edematous stage less pronounced than first stage although considerable fluid may still be present in the epidermis | Parakeratosis; acanthosis. Most of the edema has disappeared from the epidermis |
| Clinical appearance of the skin | Erythema, vesicles, papules, papulovesicles, oozing, crusting | All lesions as seen in first stage, although acuteness of condition is definitely less marked | Indurated, lichenified plaques, scales, scratch marks |
| Therapeutic indication | Drainage of edematous tissue | Drainage if still necessary. Mild astringent and soothing agents to absorb residue of exudate | Stimulation to restore skin to normal state |
| Type of treatment* | Continuous wet dressings | Wet dressings if still necessary. Pastes to absorb remaining exudate | Stimulants. Mild counterirritants |
| Therapeutic remedies | Boric acid (2%); Burow's solution (1 part to 30 parts of water); silver nitrate (⅛ to ¼%); potassium permanganate (1 part to 10,000 parts of water or 1 part to 30,000 parts of water); infusion of chamomile tea† | Lassar's simple zinc paste (without salicylic acid) with added medicaments (see below); shake lotions (evaporating) containing zinc oxide, or magnesium carbonate, talc, in various combinations. Zinc oil‡ | The tars, 1 to 10%; ichthammol, 3 to 6%; tar ointment, N.F., 25 to 50%; crude coal tar, 6% or full strength; naftalan, 1 to 10% in ointment or lotion. Salicylic acid 3 to 10%, added if necessary as keratolytic |

*Antipruritics may be indicated at any time during the course of eczema. Among such remedies may be mentioned phenol, ¼ per cent, and menthol 1/10 to ¼ per cent, alone or in combination for their synergistic effect; and benzocaine, 1 to 5 per cent. All of the tars possess antipruritic property. Roentgen rays (36 R.) may be given by the dermatologist at weekly intervals for four doses for their antipruritic effect. The antipruritic effects of a 2 per cent ointment of Pyribenzamine are as yet not definitely established. It should be pointed out that benzocaine has a high sensitizing index and should be used cautiously.

†Chamomile is official in the National Formulary, ed. 8, under the title Matricaria. The use of chamomile tea as a wet dressing for the acute and subacute stages or eczema was first brought to my attention by Dr. Max Jessner of the Skin and Cancer Unit, New York. Infusions of chamomile flowers as a wet dressing are particularly useful when continuous wet dressings are indicated and when other topical wet dressings are poorly tolerated by the patient. Chamomile tea may be prepared by pouring one quart (1,000 c.c.) of hot water upon four heaping teaspoonfuls of the chamomile flowers, contained in a suitable receptacle; the latter should then be covered for a period of approximately ten minutes. The infusion is then strained through several layers of muslin, allowed to cool and applied in the form of a wet dressing. Prepared in the manner described, the infusion has a light pink color.

‡Zinc oil consists of 40 parts of zinc oxide, to which are added 60 parts of olive oil (U.S.P.). This preparation should be dispensed in a wide-mouth bottle.

be accomplished by wet dressings applied to the lesions. I prefer either dressings of solution of boric acid or of Burow's solution, with boric acid as the favorite because it is always available, inexpensive, and quickly prepared. It should be used as a 2 per cent solution. (The saturated solution, 4 per cent, is unsatisfactory because it cakes and so interferes with proper drainage.) Burow's solution should be diluted one part in thirty for infants, one part in twenty for children. Where edema is complicated by secondary infection, the use of potassium permanganate in concentrations of 1:10,000 or in baths, of 1:20,000, is serviceable. But of all topical remedies employed as wet dressings, chamomile tea is by far the best. Wet dressings should be applied at room

temperature and kept continuously wet. Several layers of gauze (not cotton) should be used to soak up the solution. The compresses should be employed for a period of twenty-four hours at least and frequently for as long as seventy-two hours although rarely for longer than that period.*

*Representative Prescriptions*

1.—℞ Potassium Permanganate Tablets, N.F. 0.3 Gm.
Mitte Tales No. XII
Sig. Thoroughly dissolve one tablet to three quarts of water. Continuous wet application.

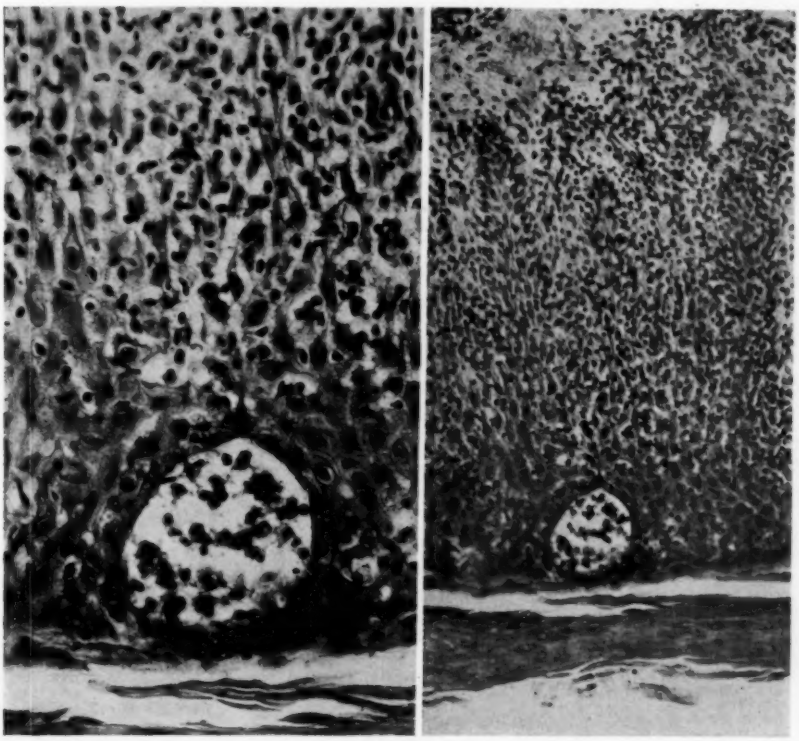

Fig. 4. Fig. 5.

Fig. 4.—Acute eczema. A marked cellular reaction is seen about the vessels of the upper cutis, in the papillary bodies, and accompanying the edema into the epidermis (exocytosis). The infiltrate is of the banal type and composed mostly of small round cells. As a result of the severe edema, the epidermis is poorly stained and a vesicle has been formed in the upper epidermis. Magnification 192.5. ×.

Fig. 5.—Acute eczema. A marked parenchymatous and interstitial edema is evident in the epidermis. The basal cell margin has been washed out. The cells are large and swollen. The excessive fluid has forced the cells apart (spongiosis). Rupture of many of the intercellular bridges has caused small holes and one vesicle to form within the epidermis. Small round cells which have accompanied the edema from the underlying cutis are visible between the epidermal cells. Magnification 498×.

*Many dermatologists prefer to cover the gauze employed as a wet dressing with some kind of impermeable dressing, such as wax paper, gutta percha tissue, or oiled silk. Under such arrangement the wet dressing shonld be renewed every three or four hours.

2.—℞ Aluminum Acetate Solution, N.F.* 1,000 c.c.
Sig. Add two tablespoonfuls to one quart of water. Continuous wet application.

3.—℞ Solution of Silver Nitrate ⅛ to ¼%
Sig. For use as wet dressings.

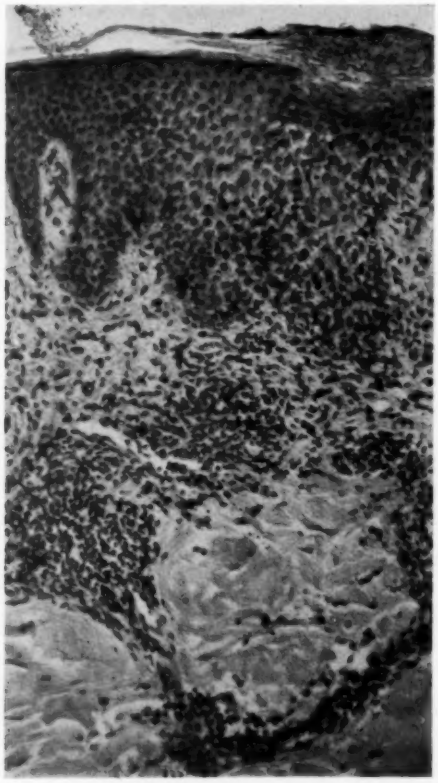

Fig. 6.—Acute eczema. The edematous change in the epidermis is well illustrated by the poor staining quality (lighter color) especially noted in the center of the section. There is a washing out of the basal cell layer of the epidermis. The inflammatory reaction is largely focal i.e., it is centered around the blood vessels in the upper cutis. Magnification 192.5 ×.

*The Second Stage.*—The second stage may properly be called the subacute stage; and while there intervenes no clear division histologically between this stage and the first nor between this and the third, certain clinical manifestations warrant its theoretical classification. It is well to remember that the pediatrician dealing with eczema is treating an acute-chronic dermatosis, which runs a varying course, now better, now worse. Indeed, most eczemas are prolonged,

*Domeboro Tablets (Dome) are a convenient means of preparing Burow's solution; the chief advantage over the official solution is that the solution may be prepared extemporaneously. One tablet added to one-half pint of water yields a 1:10 Burow's solution. This solution should be diluted one or two times for infants and children.

and acute exacerbations are by no means uncommon. Where then does the acute process end and the subacute process begin? Clinically one can be reasonably certain that the acute inflammatory process is over when the lesions are no longer "wet"—that is, when oozing has for the most part ceased and the acute erythema has subsided. Histologically it is by no means possible to divide the subacute process from the acute process because the edema remains evident even long after the acute process has run its course. However, progress can be measured in the epidermis by manifestations that should be less severe than in the first stage.

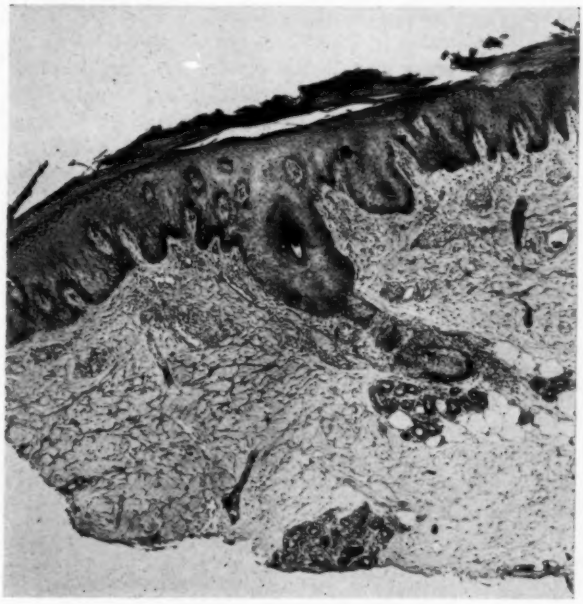

Fig. 7.—Chronic eczema. The following characteristics are illustrated: (1) Interstitial and parenchymatous edema, indicated by poorly staining areas in the epidermis; (2) acanthosis (hypertrophy) of the epidermis; (3) disorganization of the stratum granulosum; (4) increase of the stratum corneum (partly), with retention of nuclei within the horny scale (parakeratosis); (5) subsidence of the acute diffuse inflammatory reaction, which has been replaced by a moderate cellular infiltration (small round and wandering tissue cells) about the vessels of the upper cutis and the capillaries of the papillary bodies. Magnification 125 ×.

Itching should be less intense in the second stage although still persistent. Rational treatment will consist of aid to nature in removing inflammation and edema which remain in the epidermis. At this juncture pastes have a particular usefulness, prescribed either alone or in combination with one of the milder tars. It should be remembered that at this stage drainage is still going on through the epidermis although not to the extent that it occurred during the first stage. Accordingly the therapeutist must bear in mind not to thwart nature in her act of ridding the epidermis of the residual fluid by the application of ointments. Pastes too, when applied, should be spread thinly upon the gauze so that the gauze may still absorb the edematous fluid as it seeps through the

skin. For that reason some dermatologists prefer "shake lotions" to pastes at this point. There is no contraindication to the use of antipruritics if such are called for, or to the use of a mild antiseptic and germicide, which may be added to the paste or the "shake lotion," as the case may be.

*Representative Prescriptions*

The following prescriptions are suggested for ordering pastes and "shake lotions" during the interim of the acute and chronic stages of eczema:

4.—Basic Formula for a Paste:*

| | |
|---|---|
| ℞ Zinc Oxide | 25 Gm. |
| Starch | 25 Gm. |
| White Petrolatum | 50 Gm. |
| Misce et fiat pasta. | |
| Sig. Apply upon gauze or lint twice daily; bandage. | |

5.—℞ Menthol ¹/₁₀%
Coal Tar† 2%
Zinc Oxide Paste, N.F. 60 Gm.
Misce et fiat pasta.
Sig. Apply upon gauze or lint twice daily; bandage.

6.—*Basic Formula for a "Shake Lotion":*

| | |
|---|---|
| ℞ Zinc Oxide | 15.0-20.0 |
| Talc | 15.0-20.0 |
| Glycerin | 20.0 |
| Distilled Water or Alcohol (30%) q.s. ad | 100.0 |
| Misce et fiat lotio. | |
| Sig. Paint on parts three times daily. Shake well before applying.) | |

7.—℞ Ichthammol 2.0
Coal Tar Solution, N.F. 3.0
Zinc Oxide 15.0-20.0
Talc 15.0-20.0
Glycerin 20.0
Distilled Water or Alcohol (30%) q.s. ad 100.0
Misce et fiat lotio.
Sig. Paint on parts three times daily. (Shake well before applying.)

The seventh prescription contains in addition to the ingredients of the basic lotion, ichthammol (ichthyol) and solution of coal tar, which serve as a mild antiphlogistic and antipruritic. The glycerin (which is really a trihydroxy-alcohol) also helps to suspend more equally the ichthammol and other ingredients. It is permissible to add ¹/₁₀ per cent menthol or ¼ per cent phenol, or both, for synergistic effect when additional antipruritic effect is desired.

*The Third Stage.*—Last to be discussed is the so-called chronic stage of atopic dermatitis. This stage, in which the lesions consist of indurated,

*This prescription is the official Lassar's paste of the National Formulary, appearing there (ed. 8) under the title *Pasta Zinci Oxidi.*

†The strength of the crude coal tar may gradually be increased to 6 per cent.

lichenified plaques seen particularly over the antecubital and popliteal areas, is well known to pediatricians. Not infrequently these lesions are superimposed by the secondary infection. Formerly this type of dermatosis was known as squamous eczema. Histologically it is characterized by an acanthosis and interstitial and parenchymatous edema, an increase in the horny layer (parakeratosis), and a moderate cellular infiltration which surrounds the vessels of the upper cutis and the superficial capillaries of the papillary bodies (see Fig. 7).

During the chronic stage of eczema the employment of such measures as will alter the status of the skin and return it to a normal state is indicated. Agents for this purpose are regarded as of the nature of keratolytics and local skin stimulants—that is to say, as remedies that operate in a physiomechanical fashion. Some believe that the improvement following the use of these remedies and devices results from the production of a hyperemia of the skin, which, in turn, summons up the immunologic response of the skin. Older dermatologists produced the effect by the use of the popular flaxseed poultice or by the local application of a 12 per cent salicylic acid ointment, the ointment being allowed to remain upon the lesions for a period of five to ten minutes. Today dermatologists prescribe ointments and lotions containing a tar, to produce the therapeutic effect. Generalized exposure with suberythema doses of ultraviolet light from a mercury vapor quartz lamp as an adjunct to local therapy is advantageous and is prescribed routinely in all infants and children.

Antipruritics may be added, and when called for they should be ordered in mild concentrations. Any of the following antipruritics, either alone or in combination, may be added to the previously given prescriptions:

| | |
|---|---|
| Phenol | ½ to 2 per cent |
| Menthol | 1/10 to ¼ per cent |
| Ichthammol | 2 to 5 per cent |
| Solution of Coal Tar | 3 to 5 per cent |

Among the tars, I prefer the following, which I have used with gratifying results:

Ichthammol—2 to 6 per cent in zinc ointment or in Lassar's paste.
Crude Coal Tar—3 to 6 per cent in Lassar's paste.
Pine Tar—in the form of the official pine tar ointment in 25 per cent strength for smaller infants and 50 per cent for older infants and children, in a zinc oxide ointment base.
Solution of Coal Tar—5 to 10 per cent in a simple shake lotion.

I have obtained equally good results from coal tars and wood tars. However, my remedy of choice in prewar days (it has since been unobtainable) was naftalan.* I used it in the proportion of 6 per cent, which I gradually increased to 10 per cent, in simple Lassar's paste. The results from its use were most gratifying, indeed, unequalled by those obtained from the use of any similar

*Naftalan, naphthalan (Stiewe). The original Russian product was distributed by Ft. Dearborn Drug & Chemical Co., Inc., 126 West Main Street, Louisville, Ky.

℞ Naftalen (Donner) 7.2— 12.0
Zinc Oxide Paste, N.F. 120.0—120.0
Misce et fiat pasta.
Sig. Constant application to the skin.

preparation. I have since substituted the Naftalen (Donner) in its place but cannot say that it is therapeutically as effective as was the original product.

Crude coal tar is employed in 3 per cent strength in the familiar zinc oxide-starch-petrolatum base, and gradually the strength is increased to 6 per cent. It is applied interruptedly, night and day. If the lesions are upon the face, a mask may be useful in keeping the ointment in place. Crude coal tar may also be used as a paint in full strength.[3]†

It is best to renew the ointments constantly, removing the old ointment before each new application by means of a bland, nonirritating oil such as warm olive oil or sweet almond oil. The pine tar ointment previously mentioned is particularly useful in young infants with atopic dermatitis. Since pine tar ointment, U.S.P., contains wool fat, it should not be prescribed for infants or children who are allergic to wool. For them, ordinary petrolatum and not cholesterinized petrolatum should serve as the ointment base. Ellis[4] has recently shown that patients who were sensitive to ointment bases and proprietary preparations containing cholesterol as well as wool fat were frequently sensitive to such pharmaceutical bases because of the cholesterol contained in such remedies.

*Representative Prescriptions*

| | | |
|---|---|---|
| 8.—℞ | Coal Tar | 30.0 |
| | Sig. Paint upon the skin. When dry, apply unscented, purified talc. Bandage. | |
| 9.—℞ | Pine Tar Ointment, U.S.P. | 8.0-30.0 |
| | Zinc Oxide Ointment | 60.0 |
| | Misce et fiat unguentum. | |
| | Sig. Constant application. | |
| 10.—℞ | Ichthammol | 1.8-3.6 |
| | Zinc Oxide Ointment q.s. ad | 60.0 |
| | Sig. Constant application. | |
| 11.—℞ | Coal Tar | 7.2-12.0 |
| | Zinc Oxide Paste, N.F. | 120.0-120.0 |
| | Misce et fiat pasta. | |
| | Sig. Constant application. | |

Another prescription which has been frequently used in recalcitrant cases of infantile eczema, especially of the face, and in eczema of younger children is a modified Wilkinson's ointment, employed by S. Jessner under the name of "Pasta Nigra." The paste contains the following ingredients:

| | | |
|---|---|---|
| 12.—℞ | Precipitated sulfur | 10.0 |
| | Medicinal Soft Soap, N.F. | 20.0 |
| | Zinc Oxide Paste, N.F. | 20.0 |
| | Coal Tar or Juniper Tar, U.S.P. | 10.0 |

†Sulzberger[1] writes as follows concerning the use of crude coal tar in the treatment of infantile eczema: "I have found direct application of undiluted tar, painted directly on the face—a thick layer covered with purified talc—to be one of the very best of all methods of treatment. This method of application has in my hands been not only more effective but also, on the whole, less likely to irritate than any other remedy. The tar should be left on from one to three days, and then a face mask with yellow or borated petrolatum should be applied for twenty-four hours. The tar painting should then be repeated, the layer to be left on for another two, three or four days, again followed by a day of lubrication. This procedure can be repeated several times more if necessary. (The baby should not be exposed to sunlight when tars in any form or other sensitizing agents are used.)"

To prepare this ointment properly the first three ingredients should be mixed *secundum artem;* then the crude coal tar or oil of cade should be incorporated thoroughly until a smooth, homogeneous ointment results.

According to S. Jessner, the ointment is applied to the face by means of a mask, or if applied to other parts of the body, properly bandaged. After twenty-four to forty-eight hours one finds the skin mostly dry and the paste adherent. Without cleansing the skin the paste is reapplied over the former application and continued in this manner until the skin exfoliates. Then after the skin has peeled, it is cleansed every two or three days by the gentle application of purified benzine or by means of warm olive oil. The paste is then reapplied. After another two or three days the paste is reduced in strength by adding additional amounts of zinc oxide paste; after the first two weeks equal parts of the pasta nigra and zinc oxide paste are used. A week later the paste is reduced still further to one fourth the original amount of the pasta nigra, to which is added three times the original amount of zinc oxide paste. The procedure as outlined above must be continued until the skin has returned to a nearly normal state and until the itching has disappeared. As a final step to complete the therapy, 2 per cent ichthammol in zinc paste should be ordered. Of course, frequent urinalyses should be carried out while the patient is receiving the topical applications of the modified Wilkinson ointment. I have employed the preparation in the manner described and can praise its therapeutic virtues for atopic dermatitis in infants.

To complete the discussion, still another remedy deserves mention—Vioform (Ciba), which chemically is 5 chloro—7 iodo—8 hydroxyquinoline. It has not enjoyed the popularity it merits although it is official in the National Formulary, ed. 8. Its results in the treatment of infantile eczema, as well as in the eczemas of older children, have been found good by others as well; in fact, on occasions it has proved to be the topical answer to eczema when orthodox treatment with the tars has failed. It may be used in strength of 1 to 3 per cent in ointment form, either with zinc paste, zinc ointment, or with ordinary petrolatum. It is also on the market as a 3 per cent cream—i.e., in a washable base, which makes it a satisfactory remedy.

| | | |
|---|---|---|
| 13.—℞ | Vioform | 1.8 |
| | Petrolatum | 60.0 |
| | Misce et fiat unguentum. | |
| | Sig. Apply. | |

Antipruritics may be added to any of the prescriptions given.

Roentgen therapy is certainly worth a trial after all other measures commonly adopted in the management of eczema have failed to bring about improvement. The dosage under such circumstances should be small—i.e., 36 roentgen units of low voltage radiation. It should be emphasized that treatment by means of roentgen rays should be carried out only by a skilled dermatologist who has been trained in their use and not by the pediatrician.

The use of the newer antihistaminic agents for the pruritus deserves brief comment. Benadryl and Pyribenzamine have at times helped to overcome the itching of which patients complain, but they have not proved useful to the same extent as in urticaria.

## CONCLUSION

An attempt has been made to outline a simple and practical plan for managing atopic dermatitis in infants and children. Because all rational therapy must be based upon a clear understanding of the underlying pathologic changes, reference has been made to the fundamental principles of the dermatosis, both in its etiology and its mechanism of development. It appears that there is seldom need for the use of proprietary remedial agents in the management of atopic dermatitis because, happily, the dermatosis in all its stages can be treated adequately by chemicals and remedies contained either in the *United States Pharmacopeia* or the *National Formulary*. Further it appears that a few proved remedies judiciously employed are capable of doing more good than a large number of preparations employed without clear-cut indications for their use.

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# Clinical Conference

## CONFERENCE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

PAUL V. WOOLLEY, JR., PEDIATRICIAN-IN-CHIEF

### Case 1. Eczema Vaccinatum

DR. E. BRYCE ALPERN (Resident in Pediatrics).—This 14-month-old white child was admitted three days ago because of a rash of five days' duration. He has in the past had both asthma and eczema, but the latter has been manifest lately only by thickening and induration over the face and flexor surfaces of the extremities. Ten days ago he became irritable, lost his appetite, and passed several watery stools. Two days later a crop of "blisters" appeared on the areas involved earlier by eczema, and he was feverish and vomited several times. There were no eruptions in the remainder of the family, but a brother, with whom he was in intimate contact, had been vaccinated some thirteen days before appearance of the vesicles.

The patient was quite ill on arrival here, unhappy, and with a temperature of 102° F. The areas usually accentuated in infantile eczema—the face, elbows, and knees—were confluent masses of pustules resembling individually primary takes of eight or nine days' duration. Umbilication was present on most, but a few remained smooth while none resembled the earlier stages of vaccinia. Adenopathy was generalized and most marked in the axillae, where the nodes formed large tender masses. The trunk and other areas not predisposed by eczema were free from involvement. Laboratory data obtained on the day of admission include a normal urinalysis, 5.9 Gm. per cent of hemoglobin, and 51,000 white blood cells per cubic millimeter, of which 49 per cent were eosinophiles and 32 per cent neutrophiles showing marked toxic changes. The cerebrospinal fluid was normal in all respects.

On the day following admission the patient was worse and remained extremely irritable despite sedation and a return of the temperature to normal. Treatment had included a transfusion, 10 ml. of gamma globulin intramuscularly, full doses of penicillin and sulfadiazine, and a cellophane-heat cradle technique for protection of the skin. Yesterday he continued to deteriorate, and his temperature fluctuated widely. Several loose stools were passed, and during the afternoon he became quite dyspneic. This last development posed the question of acidosis, central stimulation, or decreased alveolar aeration. A plasma bicarbonate was 13 meq. per liter and the blood pH, 7.32, while a chest film showed no parenchymal pathologic change, and the cerebrospinal fluid was again not abnormal. The child was therefore handled conservatively, given sodium lactate and adequate fluids parenterally, and placed in an oxygen tent.

Today he is still comatose, his temperature remains unstable, and the eruption differs from that described on admission only by being three days closer to maturation (Figs. 1 and 2).

DR. PAUL V. WOOLLEY, JR.—This story illustrates the often repeated and often broken dictum: Do not vaccinate the contacts of eczematous babies. Our knowledge of several epidemiologic phases of eczema vaccinatum is incomplete, but in this instance, at least, we can reconstruct the story. (1) The sibling was vaccinated, responded with a primary take, and on the fifth day became involved with the systemic exanthematous disease, vaccinia; remember that this disease does not remain localized to a little spot on the arm but invades the host like other virus diseases. (2) Elementary bodies from this child were then passed to our patient and came to lodge on the skin areas previously prepared by eczema.

Fig. 1.—Eczema vaccinatum.

How this transmission was effected mechanically is open to interpretation, but the infecting particles are known to be present in both the developing pock and in the respiratory droplets. (3) As a result of these local implants our patient developed, some three days later, systemic evidences of vaccinia and, two days following, the cutaneous evidences of a primary take.

The treatment employed can be divided into three phases. First, he was given blood, plasma, and gamma globulin in the rather forlorn hope of modifying favorably the symptoms of vaccinia, per se. Several years ago we received a patient who had the misfortune to inoculate his conjunctiva at the time of vaccination so that the papular stage was reached in the eye and on the arm at the same time. Blood was obtained from a recently vaccinated individual, and

with this the patient was transfused. The papules at both sites underwent development resembling the classical "accelerated take" and did not scar. This led to such brief animal experimentation as the situation allowed, and we were able to show that in rabbits the use of human immune serum would prevent a take when injected during the incubation period and would prevent metamorphosis when used in the papular stage. We had no success in modifying the course of the primary take thereafter and hence, in the present patient, held little hope of benefit. Second, attempts to prevent secondary involvement of the damaged

Fig. 2.—Eczema vaccinatum.

skin by pyogenic organisms should be instituted, in this case by the use of penicillin and sulfadiazine. Finally, such supportive measures as will insure adequate fluid and electrolyte intake, optimal pulmonary ventilation, and stabilizaton of temperature should be considered. In the present patient we are still somewhat at a loss to explain the hyperpnea, and it is most likely a combination of central changes and mild acidosis. So far as the prognosis is concerned, I have little hope for this infant. In the excellent review by McKhann and Ross[1] a mortality of 30 per cent was anticipated, and the wide involvement, extreme toxicity, and failure so far to respond to therapy are not encouraging.

QUESTION.—What is the relation of eczema vaccinatum to Kaposi's varicelliform eruption?

DR. WOOLLEY.—I suppose that a liberal interpretation of Kaposi's description would justify placing cases of eczema vaccinatum in his syndrome, but he was more likely referring to the disseminated lesions of herpes simplex, from what we know today. He would certainly have recognized the similarity of this disease to the natural evolution of cowpox.

DR. JAMES L. WILSON (Professor of Pediatrics, the University of Michigan).—I think Kaposi's description covers best the clear vesicular eruptions seen in babies with any excoriated skin lesion. We see it as well in those with diaper rashes as eczema, and it is usually due to herpes virus or similar strains.

QUESTION.—Would the use of intracutaneous vaccination tend to avoid this complication?

DR. WOOLLEY.—Calf vaccine cannot be rendered sterile and should never be given intracutaneously. Vaccine propagated in tissue culture and eggs has been used but has not received wide acceptance. In any case it is difficult to see how its use would prevent spread since it is most probable that the vaccine particles are disseminated by the respiratory secretions.

QUESTION.—How can the diagnosis of eczema vaccinatum be established in the absence of a history of contact?

DR. WOOLLEY.—Vaccinia can be differentiated from all viruses other than variola quite simply by two means. When lymph from an active lesion is inoculated into the cornea of a rabbit, a typical lesion develops and the specific inclusions can be identified on section. A precipitin test, utilizing the lymph and a prepared antiserum, has been described by Paul and is quite specific.

*Final Note*

This patient died on the day following presentation and was discussed at the weekly Clinical Pathological Conference of Dr. W. W. Zuelzer. A surprise finding was an extensive pulmonary process, which had not been detected clinically and which undoubtedly explained to a considerable extent the hyperpnea noted during life. The exact nature of this was not clear although the distribution fitted an aspiration pneumonia better than an infectious process. Two patients with eczema vaccinatum seen since this one have survived, but neither had the widespread confluent lesions described in this child.

**Case 2. Rickets Resistant to the Usual Doses of Vitamin D**

DR. WOOLLEY.—Since this patient has not been in the hospital recently, it will save time if I review the history. He is now 25 months old and was seen here first some five months ago because of rickets. During the first eleven months of life he had developed normally, and nothing out of the ordinary had been noted either by the parents or his physician. He then stopped standing or attempting to walk, although both levels had been attained earlier. For the next

four months he appeared increasingly unhappy and seemed, at times, to have pain in his legs, and he ceased even to creep. In March, 1947, when he was 15 months of age, x-ray films of the extremities were said to show rickets although daily doses of percomorph oil in roughly 1,500 unit amounts had been given since the child was 3 weeks of age. During the summer of 1947 he was given 9,000 units of vitamin D daily, one third as percomorph oil and the remainder as viosterol, as well as thorough exposure to sunlight, but no clinical or roentgenologic evidence of healing appeared. Dr. Glen Hause, one of our staff physicians, saw him in September, 1947, and brought him here for study; we have followed him together since that time.

A review of his family and past histories has not been helpful except that the mother has kept admirable records which support her contention of normal growth and development prior to 11 months. Physically, at 20 months, he was rather small, measuring 29.5 inches and weighing 30 pounds. He was well nourished for his size but the musculature felt soft and relaxed, while bowing of both the arms and legs was grossly obvious. His head was well formed and free from stigmas, but the ribs flared and beading of the costochondral junctions was pronounced. The abdomen was prominent and the wall thin. When supported he would stand and even take a step or two in a waddling and unenthusiastic manner. Films obtained at admission (Fig. 3) will be shown shortly by Dr. Evans; they confirmed the impression of active rickets.

Our immediate study of this child followed the lines stressed in these clinics on several occasions. Renal disease was discounted by several normal urinalyses including specific gravities of over 1.025, by blood urea determinations consistently within the usual ranges, and by good concentration of Diodrast. There was nothing to suggest liver dysfunction, if such per se is ever the cause of rickets, since both the prothrombin level and the cephalin flocculation tests were satisfactory. Blood calcium levels consistently below 8 mg. per cent accompanied by blood phosphorus determinations ranging from 1 to 3 mg. per cent are not typical of any parathyroid disorder, while absence of cystine crystals, urine free from sugar or albumin, and a normal bicarbonate content of the blood did not suggest the Fanconi syndrome or a "metabolic defect." This then left us with two plausible possibilities, a failure to absorb vitamin D from the intestine, or a failure to respond to the usual levels of absorbed vitamin. The first was discounted temporarily by inference since there was no difficulty in absorbing fat and since vitamin A was adequately handled; later this was ruled out definitely by giving vitamin D intramuscularly without healing. We therefore began to give increasingly large doses of vitamin D orally and to follow the child's progress periodically with blood calcium, phosphorus, and phosphatase determinations as well as with monthly roentgenograms.

During October he received a total daily intake of 75,000 units, of which one-third was percomorph oil and the remainder viosterol. Five grams of calcium lactate were given concomitantly. At the end of the month there were no changes in the films, the blood calcium and phosphorus were still reduced, and the phosphatase remained at 30 Bodansky units, where it had been during hospitalization. Early in November an additional 25,000 units as percomorph

oil were given, but this, as might be expected, resulted in gastrointestinal symptoms so that he received during the remainder of the month 100,000 units as viosterol and 25,000 units as percomorph oil. During this period the parents were instructed to offer orange juice liberally, and the child's daily consumption was usually around 16 ounces. Some response was obtained on this regime since by December the blood calcium was 10 mg. per cent and the phosphorus 3.8 mg. per cent. No positive evidence of healing was reported roentgenoscopically, and the phosphatase was 67 Bodansky units. During December he was given, in addition to orange juice and calcium salts, 150,000 units of viosterol and 25,000 units of percomorph oil, and today (Jan. 12, 1948) his calcium is recorded as 9 mg. per cent with the phosphorus up to 4.6 mg. per cent. The phosphatase has fallen to 32 Bodansky units, and Dr. Evans is able to demonstrate unequivocal evidence of healing.

DR. W. A. EVANS (Roentgenologist-in-Chief).—This film (Fig. 3), taken last September, shows marked flaring and irregularities at the ends of the diaphyses, and there has been no deposition of calcium in the metaphyseal new bone for some time. The periosteal new bone is also low in calcium content. These findings are characteristic of severe rickets of long standing, of at least ten months by our measurements. There is considerable bowing of all the long bones.

These films taken during October, November, and December show no essential deviation from those described earlier, although, in retrospect, there possibly was a little increase in density of the osteoid in the December set. Here are the films for yesterday (Fig. 4). There has been considerable ossification at the ends of all diaphyses as well as extensive alteration in the appearance of the periosteal osteoid. The metaphyseal areas remain irregular, which means that we still have not effected complete healing.

QUESTION.—What interpretation can be given the phosphatase values in this case?

DR. WOOLLEY.—These were continually elevated, with the highest value of 67 being recorded in December and falling to 32 yesterday. It is difficult at times to explain phosphatase changes, but I think if we forget specific cases and look upon it from Albright's generalization that phosphatase goes up when there is increased osteoblastic activity, such as in response to stresses on osteomalacic bone, certain discrepancies disappear. When this boy was confined to bed and had neither the desire nor the ability for weight-bearing, the phosphatase remained only moderately elevated—in the thirties. In December, when his parents reported increasing activity and marked improvement in disposition, it went up to double the former level even though the blood chemistry would suggest a state optimal for healing. Now the phosphatase has come down as healing takes place; isn't that likely to reflect decreased osteoblastic activity as the bones become mechanically better able to cope with weight-bearing?

QUESTION.—Isn't there considerable danger in using such large doses of vitamin D over a protracted time?

DR. WOOLLEY.—It has been pointed out that the greatest danger of overdose with D lies in raising the calcium level to a point where kidney damage ensues. With this patient we have not worried too much since repeated blood determinations have consistently shown a hypocalcemia. We have taken the additional

Fig. 3. Fig. 4. Fig. 5.

Fig. 3.—Resistant rickets, September, 1947.
Fig. 4.—Resistant rickets, January, 1948. Note extensive calcification with continued irregularity at the epiphysis.
Fig. 5.—Resistant rickets, March, 1948. Healing now complete.

precaution of having his mother check two specimens daily with Sulkowitch's reagent, and to date she has not detected calcium excretion. I think that now healing is proceeding we will have to be doubly cautious, and she has been warned to notify us immediately upon obtaining a positive reaction. We will then have to adjust the child to a maintenance vitamin D intake which will assure continued calcification without excessive calcium loss.

Dr. Johnston, do you have any pet theories on such patients? It is to me a fascinating fact that we have a biologic reaction which requires 250 times the

usual amount of a reagent in order to effect a comparable result—even though absorption does not seem to enter the problem. It seems almost as if some individuals did not utilize the usual form of D but required an isomer occurring as a contaminant in a ratio of maybe 1:250 in standard oils.

DR. J. A. JOHNSTON (Pediatrician-in-Chief, the Henry Ford Hospital).—I have no explanation for refractive rickets and know of no one else with any satisfactory theory. We have found that the addition of a small amount of thyroid seems to speed up healing in patients with rickets, but this is probably a nonspecific reaction since there certainly is little common to both hypothyroidism and rickets.

*Final Note, April, 1948*

Healing by x-ray is now complete (Fig. 5). On March 11, 1948, the mother reported a strongly positive Sulkowitch test and all medication was stopped. The test became negative in three days, and the child is now on 75,000 units daily and shows only occasionally a faint clouding with the reagent.

**Case 3. Amebic Dysentery**

DR. ALPERN.—This little Negro girl is now 19 months old and has been admitted because of bloody stools passed over the last four weeks. She was here for a few days earlier in the month with the same complaint but complicated by a severe upper respiratory infection, which was thought to account for her symptoms so that not enough attention was paid to other possibilities, although she was proctoscoped and nothing was found.

Her stools during the period of illness have numbered from three to twelve daily and have been of the usual color, but are frequently streaked with mucus and usually followed by the passage of about a teaspoonful of recognizable blood. They have not been tarry, and she has had no abdominal pain or loss of appetite.

Physical examination showed little to lead to a diagnosis, and the urine, blood cell counts, tuberculin test, and Mazzini test were all within the limits of normal. A stool was semiformed and streaked with blood and mucus but no pus. Cells resembling amebas were seen, and these contained red cells and agreed in size with the usual limits for *Endamoeba histolytica*. Only two cysts were found in preparations stained with iron hematoxylin, but they were quite typical of the pathogenic species. The patient was again proctoscoped, this time with a longer instrument, and near the rectosigmoid junction were found numerous discrete and punched-out ulcers, many of which were covered by gray membranes. The remainder of the mucosa was normal. Smears taken directly from the ulcers were loaded with trophozoites.

It is interesting that this child's father was in the Army and, while he was not in the war zones, did have several bouts of diarrhea. He is being treated by the Veterans' Hospital for abdominal symptoms attributed to duodenal ulcer. His physician has been contacted and will examine the remainder of the family.

DR. WOOLLEY.—This case needs little comment except to say that we all missed the diagnosis during the first admission and that infants do contract

amebic dysentery even though it more typically strikes an older age group. I have recently talked to two internists, both former service men and both on the Veterans' faculty, who tell me that there is plenty of amebic dysentery in the Detroit area, once it is looked for and once proctoscopy becomes a routine part of the gastrointestinal study. The laboratory diagnosis, as most of us who saw it in service know, is not difficult. The trophozoites occur during active ulceration and can be found in freshly passed stools or in swabbings from the lesion. The cysts are characteristic of periods when diarrhea has abated and are best studied after staining. Positive differentiation of pathogenic from the saprophytic amebas still remains a problem for the laboratory specialists. Dr. Alpern, how do you propose to treat this child?

DR. ALPERN.—It is generally recommended that Diodoquin or carbarsone be used in children rather than emetine or Yatren. We have already begun Diodoquin in daily dose of ¾ gr. per pound and will keep this up for three weeks and follow it with two weeks of carbarsone.

*Final Note*

No blood was found in this child's stools after two days' therapy, and the ulcers were found by proctoscopy to be healed at the end of one week. No complaints were elicited at her monthly return visit.

### Case 4. Pyloric Stenosis

DR. MARY JANE STERN (Resident in Pediatrics).—This 5-week-old boy was admitted yesterday because of vomiting since birth. The mother stated that emesis occurs a few minutes after almost every feeding and has gradually become more and more forceful. Stools during this period have been scanty, and a cathartic has been given daily. Treatment at home has been limited to frequent changes in the amount and constitution of the formula, but despite such measures the weight has fallen from 7 pounds, 1 ounce at birth to 5 pounds, 12 ounces on admission here.

Examination showed the child to be scrawny, hungry, and dehydrated. The respirations were shallow and very irregular. A typical pyloric tumor was easily felt, and the vomiting on trial feeding was forceful and immediate. Laboratory information included a normal urine with a pH of 9, 15.9 Gm. of hemoglobin, a normal white blood cell count, and a negative Mazzini test. The serum bicarbonate was 41.8 meq. per liter and the blood urea nitrogen 48.7 mg. per cent.

It was obvious that the patient, besides being dehydrated and in a poor nutritional state, was in severe alkalosis. He was given a mixture of oxygen and carbon dioxide by inhalation and then 90 ml. of 1/6 N ammonium chloride subcutaneously as well as plasma and glucose intravenously. The blood bicarbonate fell to 23.7 meq. per liter in six hours, the baby clinically was markedly improved, and the usual Fredet-Rammstedt procedure was carried out this morning without incident.

DR. WOOLLEY.—This patient is shown for three reasons. First, since we have become so highly sensitized to the possibility of pyloric stenosis it has be-

come a rarity to see a baby in the state of this one. Some eighty patients have been admitted for surgery in the past two years, and I believe this is the first in whom severe alkalosis was a problem; usually nothing other than mild preoperative preparation is in order. Second, we call attention to two means of controlling alkalosis—carbon-dioxide inhalations, and the more rapid and more exact technique of parenteral ammonium chloride, a method popularized largely by the St. Louis group.[2] Finally, this gives Dr. Evans the opportunity to discuss the roentgenologic diagnosis of pylorie obstructions.

Fig. 6.—Normal stomach, pylorus, and duodenum.

DR. EVANS.—In the past we have not often been called upon to demonstrate hypertrophie pylorie stenosis roentgenographically, since the story and physical findings have been considered sufficient for diagnosis. There are, however, occasions when confirmatory evidence is desirable, especially when a tumor is not palpable and a functional obstruction is under consideration or when an organic anomaly other than hypertrophic pylorie stenosis is suspected.

It is necessary, for the satisfactory study of the stomach, duodenum, and pylorus in infancy, to have the mucosal surfaces washed free of mucus and the stomach emptied of air, food, and secretions. Feedings should be withheld for twelve hours and, if the stomach appears distended, a tube should be in place during this period. Lavage is then carried out until the returns are clear. A thick suspension of barium, which will cling to the surfaces, is desirable; only about 5 to 10 ml. of this should be given. This film (Fig. 6), recently obtained

on a patient suspected wrongly to have a pyloric obstruction, shows the normal appearance of the stomach, pylorus, and duodenum. Note that the column of barium passes freely from the stomach in a sizable stream and that the pyloric impingement is of only short duration. These films (Fig. 7), in contrast, are from a patient with proved hypertrophic pyloric stenosis. The upper two films illustrate the difficulty of examination when the stomach is distended by gas and

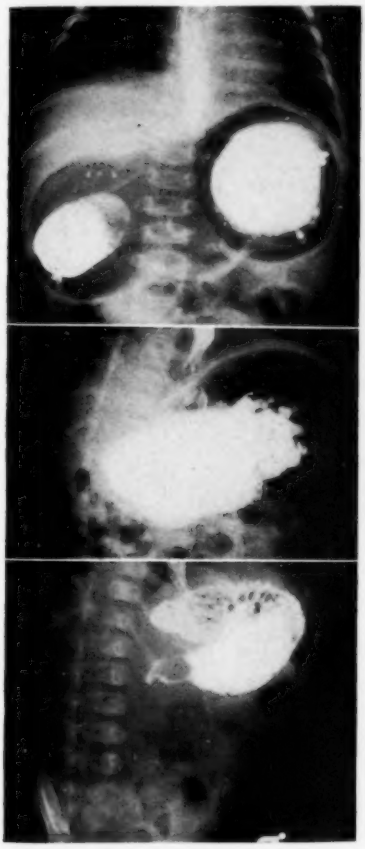


Fig. 7.—Hypertrophic pyloric stenosis. *A* and *B*, films without correct preparation, showing merely dilatation and gaseous distention. *C*, following correct preparation and now showing classical signs of pyloric stenosis.

liquid. The lower film study was made after preparation by aspiration and lavage of the stomach, and the long narrow pyloric canal is well demonstrated (the string sign). We can also see that the barium located at the pyloric end of the stomach assumes a concave aspect; this is due to impingement on the usual contour by the hypertrophied pylorus. For completion we show this film (Fig. 8), illustrating a partial obstruction within the duodenum itself. Note that the

pylorus as well as the first portion of the duodenum is normal, in contrast to the constriction seen with hypertrophic pyloric stenosis. There is gaseous distention of the descending loop of duodenum with small amounts of gas in the small bowel beyond, indicating a partial obstruction in the distal duodenal segment. At operation, peritoneal bands were found obstructing the duodenum proximal to the ligament of Treitz.

Fig. 8.—Duodenal obstruction (partial) due to peritoneal band. Note dilatation of first portion of duodenum.

QUESTION.—How much attention can you pay to the size of the stomach and to the emptying time?

DR. EVANS.—Neither is reliable. The stomach is easily distended by air, and hence size is entirely relative. So far as emptying time goes, this also is extremely variable, depending upon gastric motility and activity as well as relaxation of the normal pylorus and absence of obstruction.

DR. JOSEPH A. JOHNSTON (Henry Ford Hospital).—Even when a tumor is palpable it is important to appraise the clinical history and to resort to x-ray if a reasonable doubt exists. We have recently seen a child operated upon after all of us had felt what we took to be a tumor but which turned out to be a dilated and hypertrophied duodenum due to obstruction lower down.

DR. ALLAN RICHARDSON (Senior Pediatrician).—The ability to feel a pyloric tumor varies greatly with the individual. Dr. David Levy, the dean of pediatricians in this area, claimed that he had never palpated one with certainty. It requires for all of us a certain amount of persistence and patience but has, in my experience, been rewarded by absolute diagnosis.

DR. OTTO GROB (Senior Pediatrician).—A very important point brought out by this patient is that it is all right to handle vomiting babies with conservative medical treatment, such as phenobarbital, atropine, and thickened feedings, so long as the child is not losing ground. However, as soon as weight loss appears, it is time to institute more drastic study and to consider a truly obstructive lesion.

QUESTION.—Is there any satisfactory answer to why patients with pyloric stenosis begin to show symptoms only after several weeks of normal life?

DR. WOOLLEY.—This is a question that has received attention for years, and there is today still no concrete information on the pathogenesis of the disease and no explanation for the male predilection. We were taught, some ten years ago, that the tumor was congenital and that vomiting of a projectile type developed only after the stomach could hypertrophy. Others have long contended that the hypertrophy is present at birth but that a second element, spasm, must be added later to cause typical clinical symptoms. Still others believe that the time of onset of both hypertrophy and spasm varies and may be present before birth or develop during the first few weeks of life. We have all been interested in Dr. Wallgren's recent experiment,[3] in which he performed gastrointestinal series on 1,000 consecutive newborn boys, of whom five later developed clinical and roentgenologic evidence of pyloric stenosis. When he reviewed the original films taken on the five he could find nothing to distinguish them from the remainder of the newborn group.

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# Psychologic Aspects of Pediatrics

## PSYCHOLOGY IN PEDIATRICS

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PSYCHOLOGY as an inextricable part of medical functioning has yet to become a formal constituent of the medical curriculum. The dynamic psychology of the twentieth century introduced the neurosis as an embracing term which exonerated the physician of responsibility in those distressed cases yielding no demonstrable organic components; the organically oriented practitioner either impatiently nursed his "neurotics" along or shifted the burden to the psychiatrist. This dichotomy in treatment cannot operate in the best interest of the patient or of medical progress.

There is some doubt that the neurotic's sufferings are altogether functional; it seems likely that improved diagnostic techniques will reveal some covert organic defect in that physiologic system through which the conflict is expressed. Psychologic tests of neurotics disclose consistent impairments in mental efficiency, possibly dependent on neurological correlates. Gesell[9] expresses this succinctly: "Thought structures are just as real, just as somatic, as crystal and fiber structures. . . . The induction forces which operate at the lofty psychical level of creative thinking are subtle and complex, but they cannot be different in essence from those which shape the soma. Thought structures are in fact the ultra-electronic histology of the soma. . . . The long deferred clinical symptoms trace back to early life. As in neurology, so in psychiatry there are many genetic phenomena which can be understood only in terms of developmental mechanisms."

Whatever may prove to be the relative contribution of the organic and the psychologic in the neurotic illness, there is no doubt of the inseparable cyclical interaction in that group of diseases now labelled psychosomatic, whose manifestations are unquestionably those of somatic disease processes. That these and even infectious diseases are predisposed and exacerbated by psychic factors has been demonstrated many times. Day[3] found consistent psychic trauma previous to the development of tuberculosis in young persons. Bronchial asthma reveals a large psychogenic component.[19] According to Richardson,[16] infectious disease develops only when the individual has reached the breaking point; it is no longer easy to conceive of asthma or ulcer or obesity as a characteristic only of the individual; they must be considered as part of the family and the larger environment.

That psychologic tension plays an important role in lowering the threshold of resistance is an important clue to the possible threat of more calculable

This paper is an abridgement of a chapter which will appear in *Applied Psychology*, edited by Fryer and Henry, to be published in the near future by Rinehart and Co., New York.

environmental interrelationships. The ready response of the autonomic nervous system to mental stress in producing genitourinary and gastrointestinal difficulties, the dependence of vascular disaffections on environmental disturbances, and the fluctuation of mental level due to asthenia, endocrine imbalance, or disease process, all allow the broad generalization that "every organic disease, temporary or permanent, contains a functional factor; and every functional disorder is accompanied by some physical change of secretion, excretion or motor function which in time affects tissues."[20]

How, then, can medical practice be conducted without psychologic training? The patient at present falls between the Scylla of the organically oriented physician who usually ignores the psychologic implications, and the Charybdis of the psychiatrically oriented practitioner who often ignores the organic implications.[21]

Whatever the psychologic delinquencies in adult medical therapy, they cannot be tolerated in pediatrics. The pediatrician has access to continuous anamnesis; he is aware of the mother-child relationship; he can observe and help to shape the physical and emotional adjustment of his patient. He has the grave responsibility of anticipating the interaction of environmental pressures and constitutional weaknesses and predispositions. Without adequate guidance, a faulty interaction establishes the foundation of adolescent and adult personality and somatic problems.

Only the youngest pediatricians have received even minimum psychologic training. Short of achieving the ideal state in which the pediatrician is as learned psychologically as he is medically, the simple solution would seem to be a closer conjunction between psychologist and physician. The physician now refers only the most glaring behavior disorders to the psychologist. Not only has the rewarding period of possible prophylaxis been missed, but the situation has already been aggravated by concomitant family tension arising from the child's maladjustment.

Behavior disorders are, however, an already extreme symptom of poor integration. Less discernible are psychogenic factors in apparently organic disturbances, such as asthma, colds, diabetes, and dermatologic conditions. Eleven asthmatic children[15] presented basic conflicts revolving around an exaggerated fear of separation from the mother; there was strong evidence that the specific emotional condition was at least of equal importance to the allergic sensitivity in the production of asthmatic attacks.

In a five-year study of nursery school children,[4] the highest incidence of colds appeared in children from broken homes; anxiety and frustration stemming from traumatic situations induced internal tensions whose operation may be assumed an important factor in contributing to susceptibility. Other workers,[14] applying criteria of normality to diabetic children, discovered an earlier onset of the ailment among the markedly deviate than among the normal. Twice as many of the abnormals had frequent ketosis. Purely medical treatment of the diabetic child must therefore remain inadequate.

Dermatologic and allergic phenomena may be deeply rooted in childhood reactions to a congenital weakness. Deutsch and Nadell[7] trace several presuppositions for the development of chronic allergies and related skin conditions:

skin symptoms in early childhood probably originating on a genetic basis; a deviation or fixation of instinctual drives during the earliest psychic development and fusion of these with the different sense perceptions related to the skin; complementary neurotic traits of the environment favoring the amalgamation of the psychosomatic entity; development of a narcissistic and exhibitionistic personality pattern tinged with compulsive neurotic traits.

The permeation of psychologic factors in the child's development in illness and in health makes psychologic services as vital an adjunct to pediatrics as the tests of the medical laboratory. "The psychology of the child, which includes all his behavior, is inseparably bound up with his nervous system and indeed with his entire organism."[11]

Because of its relative novelty and because competent psychologists are few, psychologic service is, on the whole, limited to children with school maladjustments, with serious behavior disorders, and to those in penal or mental institutions. Yet the so-called normal child might yield the best guidance dividends by achieving an adjustment unsusceptible to illness, flexible to unavoidable illness without traumatic sequelae, and otherwise comfortably integrated and mature. Suranyi[18] saw noticeable differences in normal children at birth, and observed that some were from the beginning adored by everyone, some with special talents endeared themselves to a few, and some aroused antipathy in nearly all who came in contact with them. He concluded that attempts to account for these reactions on the objective basis of physical appearance or classifiable behavior were futile. There seemed to be not single gross traits but an exceedingly large number of minute factors, each too small to be regarded as significant in itself but constituting a large responsible aggregate. Many children now considered normal are in need of help; there is need of a more adequate criterion for selecting them and for the recognition of small signs of instability. Accordingly, psychologic guidance might well be a part of the routine medical checkup of even the normal, healthy child.

## THE MENTALLY HANDICAPPED

The small signs in the normal child loom large in the infant handicapped by genetic factors, uterine accidents, birth injuries, anoxia, disease sequelae or endocrine imbalance. From the beginning such a handicapped child requires medical care and supportive psychologic therapy. Without the aid of psychologic tests, it is often difficult to determine the cause and degree of mental retardation or deficiency, of personality deviation, or of speech and sensory impairment.

There is, for example, a distinct difference in the thinking processes of the mentally deficient child and of the child who shows evidence of an early acquired brain lesion. The latter stresses the functional properties of objects and the concrete elements of the situation. He elaborates on detail, changes meanings of objects to suit present associations, and is unable to move beyond the given situation in space and time; his intellectual processes appear impaired, his performance is erratic and uncontrolled. The mental defective, on the other hand, shows a test pattern more controlled and less erratic, but with a limitation in most intellectual areas.

Mental deficiency and retardation derive from a varied etiology. There may be present the simple genetic factor of inferior intelligence or the results of an Rh blood incompatibility of mother and child. The exsanguination-transfusion treatment of the hemolytic diseases as a means of avoiding mental deficiency has yet to be validated.

The encephalitides following infectious diseases, congenital paresis, lead poisoning, endocrine imbalance, defects in fetal development, birth injuries. premature birth, and malnutrition, all take a toll either in frank mental impairment and retardation, in impairment of mental efficiency, or in personality disturbances.

For many of these conditions, where actual mental impairment or retardation exists, there is little medical help. But psychologic guidance can shape the environment to provide maximum satisfactions with the patient's limited resources, to remove stresses and strains, and to lighten the complicating burden of parental guilt and unhappiness.

The effects of thyroid deficiency, if recognized and treated very early, can be somewhat mitigated. Though there is a relationship between early adequate therapy and subsequent physical development, caution is indicated in predicting mental growth. The rate of spontaneous functional progress before the initiation of treatment is a more reliable basis for intellectual prediction than either the time of beginning treatment or the dosage.[2]

The premature child will probably show mental or emotional retardation for some time, the degree of retardation depending on the degree of prematurity. Nor can it be determined at what point in the developmental cycle mental growth corresponds with chronological age. Studies of visual acuity[8] suggest some lag in the sensory development of the premature infant. Quite opposed to the theory of retardation in the growth cycle of fetal infants is Gesell's[9] unqualified observation: "Uncomplicated prematurity imposes no handicap on development. The majority of premature infants are normally endowed and, given proper care early in life, their development is entirely normal. They cannot, as children and adults, be distinguished from individuals born after a full-term gestation."

## BEHAVIOR DISORDERS

Malnutrition may exist in actuality or only in the mother's imagination. Ingestion, digestion, and elimination are the child's earliest affective associations. They may aid in establishing a warm mother-relationship, or they can become powerful weapons for punishment and revenge. Grim emphasis on feeding and toilet schedules, scolding and coaxing, lengthy and fussy eating sessions, insistence on quantitative intake or on special foods, all add up to early eating and bowel difficulties and subsequent physical and emotional complications. Many of these problems, for which she pays a high price, are rooted in the mother's own hostility and neurotic maladjustments. When pediatrician and parent recognize that each child is a variable dynamo with a uniquely constituted nervous system and an individual developmental tempo, a large number of these behavior disorders disappear.

Protests against emotional deprivation and environmental frustration take the form of emesis, breath-holding, tantrums, excessive crying, provocation of convulsions, head banging, and the like. Having achieved satisfactions subsequent to an involuntary occurrence, the child is thereafter voluntarily induced to reproduce the initial success. Effective measures are, first, a relaxed indifference to these episodes when they occur, and second, therapeutic psychologic attention to the conditions that produced them; or better still, a reversal of this order when the problem can be intelligently anticipated.

A wide assortment of other tension-releasing devices appear: Restlessness, anxiety, unnatural fears, and feelings of inferiority express themselves in nail-biting, thumb-sucking, enuresis, masturbation, hair-plucking, ties, stuttering, and other behavior patterns. All require professional attention, not only to give the child relief, but because they may be symptomatic of graver maladjustments still to come. The mother's distress and involvement in the problem automatically disqualify her for finding the solution alone.

Any of these behavior disorders may appear transiently in the normal child. But the neurotic, neuropathic, or psychopathic constitution presents them in constellation and more or less permanently. Uncertain as the somatic diagnosis now is, there is reliable evidence that physiologic correlates exist to undermine resistance to even the less harsh onslaughts of the environment. A simple illustration is the infant's undue distress after swallowing air. Most infants swallow air during feeding, but those suffering from it are the kinetic type who gulp food. Rumination is a neurosis, the elucidation of which may be puzzling.[1] The pleasure derived from it induces the repetition of a once-involuntary regurgitation; this is the familiar pattern of psychologic dynamics imposed on a substratum of somatic defect.

Hysteria, a common psychoneurosis in childhood, is marked by exaggerated impressionability and suggestibility. Disturbed visceral function, motor disorders, and distorted emotional responses are the defense mechanisms adopted to safeguard ego and preserve self-respect.

These instabilities are in some measure physical as confirmed by a study by Sherman and Jost,[17] which concluded that, in general, the neurotic appears to be much more unstable physiologically than the normal child. For the neurotic, neuropathic, and psychopathic individuals, medical and psychologic supervision are mandatory through childhood and adolescence.

Enuresis, as an expression of anxiety, sexual excitement, resistance, defiance, and immaturity, is an extremely common behavior disorder. To the well-known dynamics, Despert[5] adds the neurotic attitude of those responsible for training children in urinary control. In this group, she observed that though the enuretics ate and gained well as infants, psychomotor development was relatively late. They early experienced difficulty in expressing normal aggressive impulses and persisted in infantile demands far beyond the usual age levels. While not true in all enuretics, in some cases very early training results in overorganized personality patterns with compulsive tendencies. Enuresis rarely succumbs to physical measures alone.

The fearful child and the anxious child present different behavior syndromes. Fears develop from the trauma of actual experience and, unlike anxieties, exist on the conscious level. The child exposed, for example, to surgical operation manifests emotional sequelae definitely attributable to this experience. Prolonged night terrors are characteristic responses of the one- and two-year-olds; those above 4 often become negativistic. The presence of the mother and the administration of anesthesia before removal from the hospital bedroom will sustain the young child through a trying experience when it cannot be postponed.[13] In the face of night terrors, simple hypnagogic suggestion is often effective.

## DEAFNESS AND SPEECH DISORDERS

Deafness of any degree gravely influences personality adjustment. The totally deaf child does not progress beyond prelinguistic babbling in which utterance is unaffected by auditory impressions. Both hearing aids and rehabilitation at the earliest possible moment are recommended for total and partial deafness.

Stuttering and other forms of speech disorders have long presented a challenge. Actual structural defects remedial by surgery or palate plates are relatively rare. The victim of cleft palate is understandably resentful and humiliated, and, as a result of this, often aggressive. Speech difficulties and behavior patterns derive from clear-cut causes. Lisping, too, presents a simple diagnosis of poor dental spacing or the indulgence and perpetuation of infantile speech habits. Nasal speech may be due to polyps, adenoids, or tonsils, and slowly developing speech to poor auditory perception. Much more subtle, however, are the mutisms, disorders of articulation, and stuttering.

The speech-defective child displays a variety of personality difficulties, of which speech is only one expression. Overprotection may eliminate the need of speech, gesticulation providing a good substitute. Low or retarded intelligence influences the rate of speech development, or for protective reasons the child prefers to remain at the infantile level. Special education in a nursery school is imperative for these disabilities.

Stuttering is attributable to both physical and mental disturbance, and appears during the more stressful periods of growth: from 2 to 4 years of age when the mechanisms of speech are integrating; from 6 to 8 years when school pressures are new; and in early adolescence with its physical, emotional, and social hazards.

A recent symposium on stuttering[6] revealed a many-faceted syndrome in the production of the stuttering personality. That anxiety is primary, not secondary, to the speech difficulty is an outstanding finding. The majority of the fifty children studied made a poor social adjustment very early, even before the speech defect could be considered a serious social handicap. In addition, handedness, contrary to a prevailing concept, played no part as a single etiological factor. The subjects' families had a higher than average ratio of upper respiratory, upper digestive, and cardiovascular diseases. From this the investigators conclude that the hereditary factor might be interpreted as a

somatic selectivity influencing symptomatic choice in the stuttering individual.

In the same study, stutterers revealed a marked disturbance of motor function. Even in those children who did not present motor retardation, analysis showed a global, uniform defect in maturity of the extrapyramidal system. Rorschach patterns of the same group disclosed emotional and personality maladjustments, rigidity, great anxiety, and obsessive-compulsive traits.

Johnson[12] focuses attention on a previously neglected factor—namely, that stuttering in serious forms seems to develop after diagnosis rather than before it, and is, therefore, a consequence of the diagnosis. This may imply that formal medical recognition of his difficulty poses a new problem for the stutterer.

Too often parents and teachers attach disproportionate importance to the stuttering while minimizing the personality and neurological correlates of which it is only an expression. Probably underlying both the stuttering and the parental reaction, however, is a poor parent-child relationship, lack of parental response, and a resulting feeling of insecurity.

## NEED FOR PEDIATRIC-PSYCHOLOGIC COOPERATION

There seems to be little doubt that the pediatric approach must be in large measure psychologic. Pediatrician and psychologist must work together in close teamwork, not only when personality organization provokes the disease syndrome or is adversely affected by it, but when routinely guiding the apparently normal child.

Caution is in order lest a tendency to overstress the psychogenic aspects ignore the simple physiologic evidence. The myopic child expresses his discomfort in a variety of seemingly neurotic patterns. Night terrors and even asthma may result from difficult breathing arising from bad tonsils or adenoids. The apparently wilful and disobedient or suspicious child may be laboring under a hearing difficulty. Sexual derelictions may begin with itching, irritation, or inflammation of the genital area. Inattention, lassitude, and indifference can often be laid to malnourishment or fatigue. The psychologist shares with the pediatrician, therefore, the obligation to consider all the possible factors before exercising his special skills.

Because the dynamics of the young personality are not yet clouded over by the cornified layers of resistance to social pressures and conformity, simple psychologic measures usually suffice. In many cases, therapeutic hours spent with the parents are more rewarding than those spent with the child.

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# Comments on Current Literature

## ATOPIC ECZEMA AND BRONCHIAL ASTHMA

THE relationship between atopic eczema in infants and respiratory allergy, especially bronchial asthma in older children, is of practical importance in the over-all management of the allergic child.

In a recent article Ross and Brown[1] state that about one-third of infants with atopic eczema develop other allergic manifestations in later life. They urge that allergic children be given the advantage of protection from repeated exposure to animal danders, feathers, and house dust, since a significant number of such children will develop, within a period of months or years, positive skin tests to these inhalants associated with attacks of bronchial asthma. By employing such preventive measures, it seems reasonable that a certain number of children with allergic tendencies might be spared untoward clinical manifestations.

In an article entitled "Food Sensitivity in 100 Asthmatic Children," Lewis Webb Hill[2] points out, on the other hand, that the persistence of cutaneous sensitivity to food may lead to erroneous interpretation of such skin tests and may result in serious mistakes in therapy. Although positive skin tests often persist and the cutaneous reaction may be as large as it was in the beginning, there is a great tendency in allergic children to acquire tolerance to food as they grow older.

As an example of uncritical interpretation of skin testing, Hill refers to a 5-year-old child with bronchial asthma who had been placed on a ridiculous diet, based upon results of 236 tests for food. She had been found skin-sensitive to 109 foods. "The asthma was in reality due to grass and tree pollen, and she was later quite successfully hyposensitized, with no dietary restrictions whatever."[2] While Hill states that food can cause asthma in children, he emphasizes the fact that cutaneous sensitivity to food is often not correlated with clinical manifestations of allergy. He studied 100 asthmatic children between the ages of 3 and 12 years. The skin testing was done by the scratch method. In this group, there were 218 positive skin tests to food. Of these, only forty-four (20 per cent) were shown to be of etiological significance. Egg white, fish, peanut, walnut, and chocolate accounted for thirty-eight of the forty-four significantly positive tests. Twenty-four of the 100 children were known to develop asthma following the ingestion of certain foods. It was of some practical importance that in the majority of cases their mothers had been aware of this before any skin testing had been done. Positive scratch tests to 158 foods, 72 per cent of all tests done, were shown to be of no clinical significance. Twenty-two positive tests to potato were observed, but in no instance could it be shown that ingestion of potato produced bronchial asthma or any other symptom.

Hill's findings are supported by the observations of Adams,[3] who found that of 130 positive scratch tests to food only, 23 per cent were of clinical importance. Likewise, Chobot and Hurwitz[4] reported that in their studies 18 per cent of 198 positive scratch tests to food were of clinical significance.

Hill[2] concludes that "about a fifth of positive scratch tests to foods in asthmatic children are of etiologic significance" and that "sensitivity to food, which should always be taken into consideration in asthmatic children, is of relatively little importance in comparison with sensitivity to pollen, other

environmental allergens, and upper respiratory infections.'' Positive tests that were of etiological significance when the child was younger gradually become less so as the child grows older and gains increasing tolerance to foods.

In the light of these findings, it seems clear that persistence of cutaneous sensitivity to ingesta may lead to erroneous interpretation of skin tests and thereby to unnecessary and undesirable dietary restriction of the allergic child.

RUSSELL J. BLATTNER

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## SAMUEL McCLINTOCK HAMILL
### 1864—1948

Samuel McClintock Hamill died at his home in Philadelphia on May 3, 1948. He would have been 84 years of age next November. His death marks the passing of one of the finest characters who influenced the course and ideals of American pediatrics during the first four decades of this century.

During his early professional years he was an instructor at the University of Pennsylvania from which he was graduated in 1888, and from 1901 to 1919 he was professor of pediatrics at the Philadelphia Policlinic.

Early in his career he became interested in child health, and it was in this field of pediatrics that he made his important contribution. In 1915-1916 he was president of the American Association for the Study and Prevention of Infant Mortality, and later, when this organization finally emerged as the American Child Health Association, he served again as president from 1931 to 1935. In 1929 he retired from practice and from then on gave all of his time and interest to child health work. As chairman of the Section on Medical Service of the Third White House Conference in 1929, he led and inspired a large group of pediatricians and scientists in other fields in producing a monumental study and report which included all aspects of child health. Urged by the Pennsylvania State Medical Society and the Governor of the state he took the chairmanship of the Emergency Child Health Committee for Pennsylvania, and in recognition of his work in this capacity the state society presented him with an award for distinguished service. He was also given a medal by the Philadelphia Pediatric Society "for notable service and achievement in child health."

He was chairman of the Section on Diseases of Children of the A. M. A. in 1911, and president of the American Pediatric Society 1913-1914. He was a founder member of the American Academy of Pediatries and president in 1932. In 1940 the University of Pennsylvania conferred on him the honorary degree of Doctor of Science.

Dr. Hamill started his pediatric work as a practitioner giving his services to a few children and ended a distinguished career by giving them to all children in his community, his state, and in the nation. As he grew older and less active he never lost interest in pediatric affairs. When I visited with him at his home last November his mind was clear and active, and he was intensely interested in talking about current pediatric problems and developments. This was shortly before the death of Mrs. Hamill to whom he was married in 1895.

He had a closer relationship with the younger pediatricians during his life than any of the other men of his own generation. He told me once that when he was a young man he asked Dr. Jacobi how he always kept so young in spirit and in his interests, and Dr. Jacobi told him it was because he had always kept close to the younger men. Dr. Hamill took this advice to heart, and this was one of the reasons "Sam" was so loved and respected and looked up to by the group some twenty years younger. He inspired us and gave us leadership and we looked upon him as our friend and companion without the thought of age.

B. S. V.

# News and Notes

This photograph of Dr. Henry Helmholz, Chief Medical Consultant for Europe for the United Nations International Children's Emergency Fund, was taken in Vienna while he was visiting a school in the Russian zone. Many will recognize Mrs. Helmholz in the background.

# Book Reviews

**Child Care: Questions and Answers.** Children's Welfare Federation, New York, N. Y., 1948, Doubleday & Company, Inc., pp. 159. Price $2.00.

This book was prepared by a special committee of the Children's Welfare Federation of New York. Workers from the 200-odd members of the Federation submitted questions asked by parents of children from birth to 6 years of age. A special committee then selected the most frequent and important questions and in this text answers them. It covers the fields of growth, feeding, routine care, development, emotional guidance, medical care, and the special senses. The answers are clear, simply written, and in keeping with the best of present-day pediatric thought. It is by far the best text along this line we have encountered. The book should be of great value and help to workers in children's clinics and centers, to teachers in nursery schools, and to all lay individuals who are in some way responsible for the care of young children.

# Editor's Column

## THE EDITORIAL CONTROL AND POLICIES OF THE JOURNAL

In the July issue a year ago we discussed certain plans to make THE JOURNAL OF PEDIATRICS of more practical value to the man in practice. While continuing the publication of clinical and laboratory studies upon which progress depends, opportunity was afforded last year to develop the JOURNAL at the same time in a way which would make it of greater value and interest to the practitioner who is responsible for the direct care of children, whether he be a pediatrician or general practitioner. Despite a necessary increase in subscription rates due to the tremendous increase in the cost of paper and printing, the JOURNAL now has to print a thousand more copies each month than it did in the first half of 1947.

During the year a new Editorial Board, whose names appear on the cover, was appointed. The membership is made up of representative pediatricians who hold the same feeling and attitude to the desirability of the proposed changes as the Editor.

By formal agreement entered into between the Editor and Editorial Board, and the publishers, the Editorial Board has entire control of the editorial policies of the JOURNAL. That there may be no misunderstandings the Editor would like to state that the publishers have never once interfered with or made suggestions as to the editorial policies of the JOURNAL since it was started in July, 1932.

The Editorial Board is thus in entire editorial control of the JOURNAL. It is a self-perpetuating board with power to fill vacancies and to add additional members if it is deemed in the best interests of the JOURNAL. Further, the selection of the Editor is the responsibility of the Board.

The publishers have voluntarily proposed to limit the amount of paid advertising carried by the JOURNAL, and that nothing shall be advertised unless it is acceptable to the Board.

Editorially the JOURNAL will continue to discuss pediatric matters and problems, and the views expressed will represent the views of the Editorial Board, or of individuals signing editorials if approved by the Board for publication.

As Editor we take pleasure in presenting this statement as to the editorial control of the JOURNAL.

BORDEN S. VEEDER.